

**ALKYL OR ARYL SUBSTITUTED DIHYDRONAPHTHALENE  
DERIVATIVES HAVING RETINOID AND/OR RETINOID  
ANTAGONIST-LIKE BIOLOGICAL ACTIVITY**

**1. Field of the Invention**

The present invention relates to novel compounds having retinoid and/or retinoid antagonist-like biological activity. More specifically, the present invention relates to alkyl or aryl substituted dihydronaphthalene derivatives which bind to retinoid receptors and have retinoid-like or retinoid antagonist-like biological activity.

**2. Background Art**

Compounds which have retinoid-like activity are well known in the art, and are described in numerous United States and other patents and in scientific publications. It is generally known and accepted in the art that retinoid-like activity is useful for treating animals of the mammalian species, including humans, for curing or alleviating the symptoms and conditions of numerous diseases and conditions. In other words, it is generally accepted in the art that pharmaceutical compositions having a retinoid-like compound or compounds as the active ingredient are useful as regulators of cell proliferation and differentiation, and particularly as agents for treating skin-related diseases, including, actinic keratoses, arsenic keratoses, inflammatory and non-inflammatory acne, psoriasis, ichthyoses and other keratinization and hyperproliferative disorders of the skin, eczema, atopic dermatitis, Darriers disease, lichen planus, prevention and reversal of glucocorticoid damage (steroid atrophy), as a topical anti-microbial, as skin anti-pigmentation agents and to treat and reverse the effects of age and photo damage to the skin. Retinoid compounds are also useful for the prevention and treatment of cancerous and

1 precancerous conditions, including, premalignant and malignant  
2 hyperproliferative diseases such as cancers of the breast, skin, prostate,  
3 cervix, uterus, colon, bladder, esophagus, stomach, lung, larynx, oral  
4 cavity, blood and lymphatic system, metaplasias, dysplasias, neoplasias,  
5 leukoplakias and papillomas of the mucous membranes and in the  
6 treatment of Kaposi's sarcoma. In addition, retinoid compounds can be  
7 used as agents to treat diseases of the eye, including, without limitation,  
8 proliferative vitreoretinopathy (PVR), retinal detachment, dry eye and  
9 other corneopathies, as well as in the treatment and prevention of  
10 various cardiovascular diseases, including, without limitation, diseases  
11 associated with lipid metabolism such as dyslipidemias, prevention of  
12 post-angioplasty restenosis and as an agent to increase the level of  
13 circulating tissue plasminogen activator (TPA). Other uses for retinoid  
14 compounds include the prevention and treatment of conditions and  
15 diseases associated with human papilloma virus (HPV), including warts  
16 and genital warts, various inflammatory diseases such as pulmonary  
17 fibrosis, ileitis, colitis and Krohn's disease, neurodegenerative diseases  
18 such as Alzheimer's disease, Parkinson's disease and stroke, improper  
19 pituitary function, including insufficient production of growth hormone,  
20 modulation of apoptosis, including both the induction of apoptosis and  
21 inhibition of T-Cell activated apoptosis, restoration of hair growth,  
22 including combination therapies with the present compounds and other  
23 agents such as Minoxidil<sup>R</sup>, diseases associated with the immune system,  
24 including use of the present compounds as immunosuppressants and  
25 immunostimulants, modulation of organ transplant rejection and  
26 facilitation of wound healing, including modulation of chelosis.

27 United States Patent Nos. 4,740,519 (Shroot et al.),  
28 4,826,969 (Maignan et al.), 4,326,055 (Loeliger et al.), 5,130,335

1 (Chandraratna et al.), 5,037,825 (Klaus et al.), 5,231,113 (Chandraratna  
2 et al.), 5,324,840 (Chandraratna), 5,344,959 (Chandraratna), 5,130,335  
3 (Chandraratna et al.), Published European Patent Application Nos. 0  
4 176 034 A (Wuest et al.), 0 350 846 A (Klaus et al.), 0 176 032 A  
5 (Frickel et al.), 0 176 033 A (Frickel et al.), 0 253 302 A (Klaus et al.),  
6 0 303 915 A (Bryce et al.), UK Patent Application GB 2190378 A  
7 (Klaus et al.), German Patent Application Nos. DE 3715955 A1 (Klaus  
8 et al.), DE 3602473 A1 (Wuest et al., and the articles J. Amer. Acad.  
9 Derm. 15: 756 - 764 (1986) (Sporn et al.), Chem. Pharm. Bull. 33:  
10 404-407 (1985) (Shudo et al.), J. Med Chem. 1988 31, 2182 - 2192  
11 (Kagechika et al.), Chemistry and Biology of Synthetic Retinoids CRC  
12 Press Inc. 1990 p 334 - 335, 354 (Dawson et al.), describe or relate to  
13 compounds which include a tetrahydronaphthyl moiety and have  
14 retinoid-like or related biological activity. United States Patent No.  
15 4,391,731 (Boller et al.) describes tetrahydronaphthalene derivatives  
16 which are useful in liquid crystal compositions.

17 Published European Patent application Nos. 0 661 259 A1 and 0  
18 661 261 A1 (Bristol-Myers Squibb) describe further dihydronaphthalene  
19 and naphthalene derivatives which are said in the disclosures to have  
20 retinoid-like biological activity.

21 United States Patent Nos. 4,980,369, 5,006,550, 5,015,658,  
22 5,045,551, 5,089,509, 5,134,159, 5,162,546, 5,234,926, 5,248,777,  
23 5,264,578, 5,272,156, 5,278,318, 5,324,744, 5,346,895, 5,346,915,  
24 5,348,972, 5,348,975, 5,380,877, 5,399,561, 5,407,937, (assigned to the  
25 same assignee as the present application) and patents and publications  
26 cited therein, describe or relate to chroman, thiochroman and  
27 1,2,3,4-tetrahydroquinoline derivatives which have retinoid-like  
28 biological activity. Still further, several co-pending applications and

1 recently issued patents which are assigned to the assignee of the present  
2 application, are directed to further compounds having retinoid-like  
3 activity.

4 Although pharmaceutical compositions containing retinoids have  
5 well established utility (as is demonstrated by the foregoing citation of  
6 patents and publications from the voluminous literature devoted to this  
7 subject) retinoids also cause a number of undesired side effects at  
8 therapeutic dose levels, including headache, teratogenesis,  
9 mucocutaneous toxicity, musculoskeletal toxicity, dyslipidemias, skin  
10 irritation, headache and hepatotoxicity. These side effects limit the  
11 acceptability and utility of retinoids for treating disease.

12 It is now general knowledge in the art that two main types of  
13 retinoid receptors exist in mammals (and other organisms). The two  
14 main types or families of receptors respectively designated the RARs  
15 and RXRs. Within each type there are subtypes; in the RAR family the  
16 subtypes are designated RAR $\alpha$ , RAR $\beta$  and RAR $\gamma$ , in RXR the subtypes  
17 are: RXR $\alpha$ , RXR $\beta$  and RXR $\gamma$ . It has also been established in the art  
18 that the distribution of the two main retinoid receptor types, and of the  
19 several sub-types is not uniform in the various tissues and organs of  
20 mammalian organisms. Moreover, it is generally accepted in the art  
21 that many unwanted side effects of retinoids are mediated by one or  
22 more of the RAR receptor subtypes. Accordingly, among compounds  
23 having agonist-like activity at retinoid receptors, specificity or selectivity  
24 for one of the main types or families, and even specificity or selectivity  
25 for one or more subtypes within a family of receptors, is considered a  
26 desirable pharmacological property. Some compounds bind to one or  
27 more RAR receptor subtypes, but do not trigger the response which is  
28 triggered by agonists of the same receptors. A compound that binds to



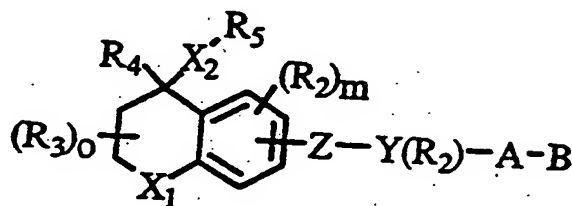
1 a biological receptor but does not trigger an agonist-like response is  
2 usually termed an antagonist. Accordingly, the "effect" of compounds  
3 on retinoid receptors may fall in the range of having no effect at all,  
4 (inactive compound, neither agonist nor antagonist), the compound may  
5 elicit an agonist-like response on all receptor subtypes (pan-agonist), or  
6 a compound may be a partial agonist and/or partial antagonist of  
7 certain receptor subtypes if the compound binds to but does not  
8 activate certain receptor subtype or subtypes but elicits an agonist-like  
9 response in other receptor subtype or subtypes. A pan antagonist is a  
10 compound that binds to all known retinoid receptors but does not elicit  
11 an agonist-like response in any of the receptors.

12 It has been recently discovered and described in a pending  
13 application assigned to the same assignee as the present application that  
14 retinoid antagonist-like activity of a compound is also a useful property,  
15 in that such antagonist compounds can be utilized to block certain  
16 undesired side effects of retinoids, to serve as antidotes to retinoid  
17 overdose or poisoning, and may lend themselves to other  
18 pharmaceutical applications as well. More particularly, regarding the  
19 published scientific and patent literature in this field, published PCT  
20 application WO 94/14777 describes certain heterocyclic carboxylic acid  
21 derivatives which bind to RAR retinoid receptors and are said in the  
22 application to be useful for treatment of certain diseases or conditions,  
23 such as acne, psoriasis, rheumatoid arthritis and viral infections. A  
24 similar disclosure is made in the article by Yoshimura et al. J Med.  
25 Chem. 1995, 38, 3163-3173. Kaneko et al. Med. Chem Res. (1991)  
26 1:220-225; Apfel et al. Proc. Natl. Acad. Sci. USA Vol 89 pp 7129-7133  
27 Augusty 1992 Cell Biology; Eckhardt et al. Toxicology Letters, 70 (1994)  
28 299-308; Keidel et al. Molecular and Cellular Biology, Vol 14, No. 1,

1 Jan. 1994, p 287-298; and Eyrolles et al. J. Med. Chem. 1994, 37,  
 2 1508-1517 describe compounds which have antagonist like activity at one  
 3 or more of the RAR retinoid subtypes.

#### 4 SUMMARY OF THE INVENTION

5 Among the compounds of Formulas 1 through 6, the present  
 6 invention covers the compounds of Formula 6. Compounds of the  
 7 remaining formulas are disclosed here inasmuch as the methods of their  
 8 synthesis pertains to the best modes of the presently contemplated  
 9 synthetic routes leading to the compounds of Formula 6. Thus the  
 10 present invention pertains to compounds of Formula 6.



Formula 1

1 wherein  $X_1$  is  $[C(R_1)_2]_n$  where  $R_1$  is independently H or alkyl of 1  
2 to 6 carbons, and  $n$  is an integer between 0 and 2;

3  $X_2$  is S or O;

4  $Z$  is  $-N=N-$ ,

5  $-N(O)=N-$ ,

6  $-N=N(O)-$ ,

7  $-N=CR_1-$ ,

8  $-CR_1=N$ ,

9  $-(CR_1=CR_1)_{n'}$  where  $n'$  is an integer having the value 0 - 5,

10  $-CO-NR_1-$ ,

11  $-CS-NR_1-$ ,

12  $-NR_1-CO$ ,

13  $-NR_1-CS$ ,

14  $-COO-$ ,

15  $-OCO-$ ;

16  $-CSO-$ ;

17  $-OCS-$ ;

18  $-CO-CR_1=CR_1-$ ;

19  $R_2$  is hydrogen, lower alkyl of 1 to 6 carbons, F, Cl, Br, I,  $CF_3$ ,  
20 fluoro substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6  
21 carbons, or alkylthio of 1 to 6 carbons;

22  $R_3$  is hydrogen, lower alkyl of 1 to 6 carbons or F;

23  $m$  is an integer having the value of 0 - 3;

24  $o$  is an integer having the value of 0 - 4;

25  $R_4$  is hydrogen, alkyl of 1 to 10 carbons, alkenyl of 2 to 10  
26 carbons and having 1 to 3 double bonds, alkynyl having 2 to 10 carbons  
27 and 1 to 3 triple bonds, carbocyclic aryl selected from the group  
28 consisting of phenyl,  $C_1 - C_{10}$ -alkylphenyl, naphthyl,  $C_1 - C_{10}$ -alkyl-

1 naphthyl, phenyl- $C_1 - C_{10}$ alkyl, naphthyl- $C_1 - C_{10}$ alkyl; CN, or

2  $(CH_2)_pCO_2R_8$  where p is an integer between 0 to 10;

3  $R_8$  is hydrogen, alkyl of 1 to 10 carbons, fluoro-substituted alkyl of  
4 1 to 10 carbons, alkenyl of 2 to 10 carbons and having 1 to 3 double  
5 bonds, alkynyl having 2 to 10 carbons and 1 to 3 triple bonds, carbo-  
6 cyclic aryl selected from the group consisting of phenyl,  $C_1 -$   
7  $C_{10}$ -alkylphenyl, naphthyl,  $C_1 - C_{10}$ -alkylnaphthyl, phenyl- $C_1 - C_{10}$ alkyl,  
8 naphthyl- $C_1 - C_{10}$ alkyl;  $Si(C_{1-6}alkyl)_3$ ,  $COR_{14}$ , camphanoyl,  
9  $C(R_{15})(R_{16})X_2R_{17}$ ;

10 Y is a phenyl or naphthyl group, or heteroaryl selected from a  
11 group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl,  
12 pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and  
13 heteroaryl groups being optionally substituted with one or two  $R_2$   
14 groups, or

15 when Z is  $-(CR_1=CR_1)_{n'}$  and  $n'$  is 3, 4 or 5 then Y represents a  
16 direct valence bond between said  $(CR_2=CR_2)_n$  group and B;

17 A is  $(CH_2)_q$  where q is 0-5, lower branched chain alkyl  
18 having 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6  
19 carbons and 1 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2  
20 triple bonds;

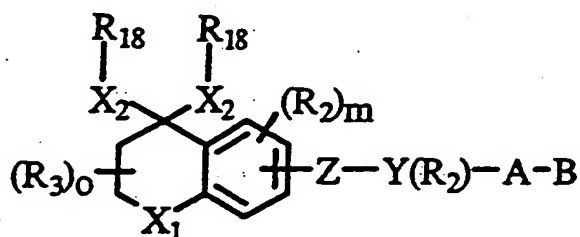
21 B is hydrogen, COOH or a pharmaceutically acceptable salt  
22 thereof,  $COOR_9$ ,  $CONR_9R_{10}$ ,  $-CH_2OH$ ,  $CH_2OR_{11}$ ,  $CH_2OCOR_{11}$ , CHO,  
23  $CH(OR_{12})_2$ ,  $CHOR_{13}O$ ,  $-COR_7$ ,  $CR_7(OR_{12})_2$ ,  $CR_7OR_{13}O$ , or  $Si(C_{1-6}alkyl)_3$ ,  
24 where  $R_7$  is an alkyl, cycloalkyl or alkenyl group containing 1 to 5  
25 carbons,  $R_8$  is an alkyl group of 1 to 10 carbons or (trimethylsilyl)alkyl  
26 where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to  
27 10 carbons, or  $R_8$  is phenyl or lower alkylphenyl,  $R_9$  and  $R_{10}$   
28 independently are hydrogen, an alkyl group of 1 to 10 carbons, or a

1 cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl,  $R_{11}$  is  
 2 lower alkyl, phenyl or lower alkylphenyl,  $R_{12}$  is lower alkyl, and  $R_{13}$  is  
 3 divalent alkyl radical of 2-5 carbons;

4  $R_{14}$  is hydrogen, alkyl of 1 to 10 carbons, alkenyl of 2 to 10  
 5 carbons and having 1 to 3 double bonds, alkynyl having 2 to 10 carbons  
 6 and 1 to 3 triple bonds, carbocyclic aryl selected from the group  
 7 consisting of phenyl,  $C_1 - C_{10}$ -alkylphenyl, naphthyl,  $C_1 -$   
 8  $C_{10}$ -alkylnaphthyl, phenyl- $C_1 - C_{10}$ alkyl, naphthyl- $C_1 - C_{10}$ alkyl, and

9  $R_{15}$  and  $R_{16}$  are hydrogen or lower alkyl of 1 to 6 carbons,  $R_{17}$  is  
 10 lower alkyl of 1 to 6 carbons, or  $R_{16}$  and  $R_{17}$  jointly form a ring having a  
 11 total of 4 to 5 carbons and the  $X_2$  heteroatom;

12 compounds of Formula 2



Formula 2

1 wherein  $X_1$  is  $[C(R_1)_2]_n$  where  $R_1$  is independently H or alkyl of 1  
 2 to 6 carbons, and  $n$  is an integer between 0 and 2;

3  $X_2$  is S or O;

4 Z is  $-N=N-$ ,

5  $-N(O)=N-$ ,

6  $-N=N(O)-$ ,

7  $-N=CR_1-$ ,

8  $-CR_1=N$ ,

9  $-(CR_1=CR_1)_{n'}$  where  $n'$  is an integer having the value 0 - 5,

10  $-CO-NR_1-$ ,

11  $-CS-NR_1-$ ,

12  $-NR_1-CO$ ,

13  $-NR_1-CS$ ,

14  $-COO-$ ,

15  $-OCO-$ ;

16  $-CSO-$ ;

17  $-OCS-$ ;

18  $-CO-CR_1=CR_1-$ ;

19  $R_2$  is hydrogen, lower alkyl of 1 to 6 carbons, F, Cl, Br, I,  $CF_3$ ,  
 20 fluoro substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6  
 21 carbons, or alkylthio of 1 to 6 carbons;

22  $R_3$  is hydrogen, lower alkyl of 1 to 6 carbons or F;

23  $m$  is an integer having the value of 0 - 3;

24  $o$  is an integer having the value of 0 - 4;

25 Y is a phenyl or naphthyl group, or heteroaryl selected from a  
 26 group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl,  
 27 pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and  
 28 heteroaryl groups being optionally substituted with one or two  $R_2$

1 groups, or

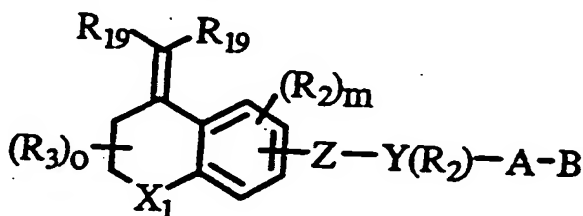
2 when Z is  $-(CR_1=CR_1)_{n'}$  and  $n'$  is 3, 4 or 5 then Y represents a  
3 direct valence bond between said  $(CR_2=CR_2)_{n'}$  group and B;

4 A is  $(CH_2)_q$  where q is 0-5, lower branched chain alkyl  
5 having 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6  
6 carbons and 1 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2  
7 triple bonds;

8 B is hydrogen, COOH or a pharmaceutically acceptable salt  
9 thereof,  $COOR_8$ ,  $CONR_8R_{10}$ ,  $-CH_2OH$ ,  $CH_2OR_{11}$ ,  $CH_2OCOR_{11}$ ,  $CHO$ ,  
10  $CH(OR_{12})_2$ ,  $CHOR_{13}O$ ,  $-COR_7$ ,  $CR_7(OR_{12})_2$ ,  $CR_7OR_{13}O$ , or  $Si(C_{1-6}alkyl)_3$ ,  
11 where  $R_7$  is an alkyl, cycloalkyl or alkenyl group containing 1 to 5  
12 carbons,  $R_8$  is an alkyl group of 1 to 10 carbons or (trimethylsilyl)alkyl  
13 where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to  
14 10 carbons, or  $R_8$  is phenyl or lower alkylphenyl,  $R_9$  and  $R_{10}$   
15 independently are hydrogen, an alkyl group of 1 to 10 carbons, or a  
16 cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl,  $R_{11}$  is  
17 lower alkyl, phenyl or lower alkylphenyl,  $R_{12}$  is lower alkyl, and  $R_{13}$  is  
18 divalent alkyl radical of 2-5 carbons, and

19  $R_{18}$  is alkyl of 1 to 10 carbons, fluoro-substituted alkyl of 1 to 10  
20 carbons, or the two  $R_{18}$  groups jointly form a ring having a total of 3 to  
21 6 carbons, or the two  $X_2R_{18}$  groups jointly symbolize an oxo ( $=O$ ) or a  
22 thio ( $=S$ ) function, or each of the two  $X_2R_{18}$  groups is H;

23 compounds of Formula 3



Formula 3

1 wherein  $X_1$  is  $[C(R_1)_2]_n$  where  $R_1$  is independently H or alkyl of 1  
 2 to 6 carbons, and  $n$  is an integer between 0 and 2;

3 Z is -N=N-,

4 -N(O)=N-,

5 -N=N(O)-,

6 -N=CR<sub>1</sub>-,

7 -CR<sub>1</sub>=N,

8  $-(CR_1=CR_1)_{n'}$  where  $n'$  is an integer having the value 0 - 5,

9 -CO-NR<sub>1</sub>-,

10 -CS-NR<sub>1</sub>-,

11 -NR<sub>1</sub>-CO,

12 -NR<sub>1</sub>-CS,

13 -COO-,

14 -OCO-;

15 -CSO-;

16 -OCS-;

17 -CO-CR<sub>1</sub>=CR<sub>1</sub>-;

18  $R_2$  is hydrogen, lower alkyl of 1 to 6 carbons, F, Cl, Br, I, CF<sub>3</sub>,  
 19 fluoro substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6  
 20 carbons, or alkylthio of 1 to 6 carbons;

21  $R_3$  is hydrogen, lower alkyl of 1 to 6 carbons or F;

22  $m$  is an integer having the value of 0 - 3;

23  $o$  is an integer having the value of 0 - 4;

24 Y is a phenyl or naphthyl group, or heteroaryl selected from a  
 25 group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl,  
 26 pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrrolizolyl, said phenyl and  
 27 heteroaryl groups being optionally substituted with one or two  $R_2$   
 28 groups, or



1 when Z is  $-(CR_1=CR_1)_x-$  and  $n'$  is 3, 4 or 5 then Y represents a  
 2 direct valence bond between said  $(CR_2=CR_2)_x$  group and B;

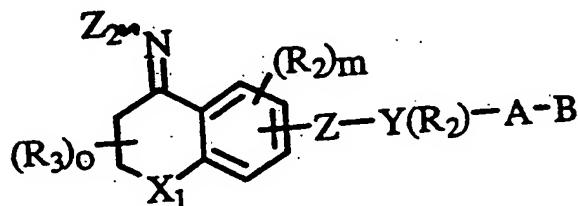
3 A is  $(CH_2)_q$  where  $q$  is 0-5, lower branched chain alkyl  
 4 having 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6  
 5 carbons and 1 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2  
 6 triple bonds;

7 B is hydrogen, COOH or a pharmaceutically acceptable salt  
 8 thereof,  $COOR_8$ ,  $CONR_9R_{10}$ ,  $-CH_2OH$ ,  $CH_2OR_{11}$ ,  $CH_2OCOR_{11}$ , CHO,  
 9  $CH(OR_{12})_2$ ,  $CHOR_{13}O$ ,  $-COR_7$ ,  $CR_7(OR_{12})_2$ ,  $CR_7OR_{13}O$ , or  $Si(C_{1-6}alkyl)_3$ ,  
 10 where  $R_7$  is an alkyl, cycloalkyl or alkenyl group containing 1 to 5  
 11 carbons,  $R_8$  is an alkyl group of 1 to 10 carbons or (trimethylsilyl)alkyl  
 12 where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to  
 13 10 carbons, or  $R_8$  is phenyl or lower alkylphenyl,  $R_9$  and  $R_{10}$   
 14 independently are hydrogen, an alkyl group of 1 to 10 carbons, or a  
 15 cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl,  $R_{11}$  is  
 16 lower alkyl, phenyl or lower alkylphenyl,  $R_{12}$  is lower alkyl, and  $R_{13}$  is  
 17 divalent alkyl radical of 2-5 carbons, and

18  $R_{19}$  is independently hydrogen, alkyl of 1 to 10 carbons,  
 19 fluoro-substituted alkyl of 1 to 10 carbons, alkenyl of 2 to 10 carbons  
 20 and having 1 to 3 double bonds, alkynyl having 2 to 10 carbons and 1 to  
 21 3 triple bonds, carbocyclic aryl selected from the group consisting of  
 22 phenyl,  $C_1 - C_{10}$ -alkylphenyl, naphthyl,  $C_1 - C_{10}$ -alkylnaphthyl, phenyl- $C_1 -$   
 23  $C_{10}$ alkyl, naphthyl- $C_1 - C_{10}$ alkyl; heteroaryl selected from the group  
 24 consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl,  
 25 thiazolyl, oxazolyl, imidazolyl and pyrrazolyl, said phenyl and heteroaryl  
 26 groups being optionally substituted with one or two  $R_2$  groups, further  
 27  $R_{19}$  is independently CN, CHO,  $CH(OR_{12})_2$ ,  $CHOR_{13}O$ ,  $(CH_2)_pCO_2R_8$ ,  
 28  $(CH_2)_pCH_2OH$ ,  $(CH_2)_pCH_2OR_{11}$ ,  $(CH_2)_pCH_2OCOR_{11}$ , where  $p$  is an

integer between 0 to 10, or the two  $R_1$  groups jointly represent 3 to 8 methylene groups which together with the alkylidene carbon complete a ring, the ring optionally containing 1 to 2 double bonds and the ring being optionally substituted with 1 or 2  $R_2$  groups;

compounds of Formula 4



#### Formula 4

wherein  $X_1$  is  $[C(R_1)_2]_n$  where  $R_1$  is independently H or alkyl of 1 to 6 carbons, and  $n$  is an integer between 0 and 2;

$Z$  is  $-N=N-$ ,

$-N(O)=N-$ ,

$-N=N(O)-$ ,

$-N=CR_1-$ ,

$-CR_1=N$ ,

$-(CR_1=CR_1)_{n'}$  where  $n'$  is an integer having the value 0 - 5,

$-CO-NR_1-$ ,

$-CS-NR_1-$ ,

$-NR_1-CO$ ,

$-NR_1-CS$ ,

$-COO-$ ,

$-OCO-$ ;

$-CSO-$ ;

1            -OCS-;

2            -CO-CR<sub>1</sub>=CR<sub>1</sub>-;

3            R<sub>2</sub> is hydrogen, lower alkyl of 1 to 6 carbons, F, Cl, Br, I, CF<sub>3</sub>,  
4 fluoro substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6  
5 carbons, or alkylthio of 1 to 6 carbons;

6            R<sub>3</sub> is hydrogen, lower alkyl of 1 to 6 carbons or F;

7            m is an integer having the value of 0 - 3;

8            o is an integer having the value of 0 - 4;

9            Y is a phenyl or naphthyl group, or heteroaryl selected from a  
10 group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl,  
11 pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and  
12 heteroaryl groups being optionally substituted with one or two R<sub>2</sub>  
13 groups, or

14            when Z is -(CR<sub>1</sub>=CR<sub>1</sub>)<sub>n</sub>- and n' is 3, 4 or 5 then Y represents a  
15 direct valence bond between said (CR<sub>2</sub>=CR<sub>2</sub>)<sub>n</sub> group and B;

16            A is (CH<sub>2</sub>)<sub>q</sub> where q is 0-5, lower branched chain alkyl  
17 having 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6  
18 carbons and 1 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2  
19 triple bonds;

20            B is hydrogen, COOH or a pharmaceutically acceptable salt  
21 thereof, COOR<sub>9</sub>, CONR<sub>9</sub>R<sub>10</sub>, -CH<sub>2</sub>OH, CH<sub>2</sub>OR<sub>11</sub>, CH<sub>2</sub>OCOR<sub>11</sub>, CHO,  
22 CH(OR<sub>12</sub>)<sub>2</sub>, CHOR<sub>13</sub>O, -COR<sub>7</sub>, CR<sub>7</sub>(OR<sub>12</sub>)<sub>2</sub>, CR<sub>7</sub>OR<sub>13</sub>O, or Si(C<sub>1-6</sub>alkyl)<sub>3</sub>,  
23 where R<sub>7</sub> is an alkyl, cycloalkyl or alkenyl group containing 1 to 5  
24 carbons, R<sub>8</sub> is an alkyl group of 1 to 10 carbons or (trimethylsilyl)alkyl  
25 where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to  
26 10 carbons, or R<sub>8</sub> is phenyl or lower alkylphenyl, R<sub>9</sub> and R<sub>10</sub>  
27 independently are hydrogen, an alkyl group of 1 to 10 carbons, or a  
28 cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R<sub>11</sub> is

1 lower alkyl, phenyl or lower alkylphenyl,  $R_{12}$  is lower alkyl, and  $R_{13}$  is  
2 divalent alkyl radical of 2-5 carbons, and

3  $Z_2$  is  $OR_1$  or  $OR_{18}$  where  $R_{18}$  is is phenyl, benzyl, lower alkyl or  
4 lower alkoxy substituted phenyl, or  $Z_2$  is  $OSi(R_2)_3$ ,  $OCOR_{14}$

5  $OC(R_{15})(R_{16})X_2R_{17}$ ,  $N(R_{14})_2$ ,  $NHCON(R_{14})_2$ ,  $NHCSN(R_{14})_2$ , where  $X_2$  is  
6 O or S;  $R_{14}$  is hydrogen, alkyl of 1 to 10 carbons, alkenyl of 2 to 10

7 carbons and having 1 to 3 double bonds, alkynyl having 2 to 10 carbons  
8 and 1 to 3 triple bonds, carbocyclic aryl selected from the group

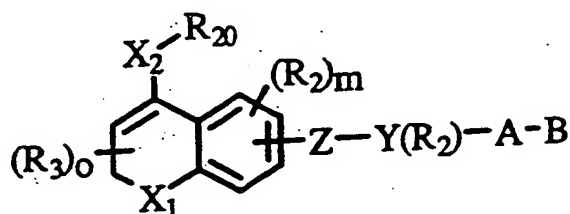
9 consisting of phenyl,  $C_1 - C_{10}$ -alkylphenyl, naphthyl,  $C_1 -$

10  $C_{10}$ -alkylnaphthyl, phenyl- $C_1 - C_{10}$ alkyl, naphthyl- $C_1 - C_{10}$ alkyl;  $R_{15}$  and

11  $R_{16}$  are hydrogen or lower alkyl of 1 to 6 carbons,  $R_{17}$  is lower alkyl of 1  
12 to 6 carbons, or  $R_{16}$  and  $R_{17}$  jointly form a ring having a total of 4 to 5

13 carbons and the  $X_2$  heteroatom;

14 compounds of Formula 5



21 Formula 5

22 wherein  $X_1$  is  $[C(R_1)_2]_n$  where  $R_1$  is independently H or alkyl of 1  
23 to 6 carbons, and  $n$  is an integer between 0 and 2;

24  $Z$  is  $-N=N-$ ,

25  $-N(O)=N-$ ,

26  $-N=N(O)-$ ,

27  $-N=CR_1-$ ,

28  $-CR_1=N$ ,

- 1  $-(\text{CR}_1=\text{CR}_1)_{n'}$ - where  $n'$  is an integer having the value 0 - 5,
- 2  $-\text{CO}-\text{NR}_1-$ ,
- 3  $-\text{CS}-\text{NR}_1-$ ,
- 4  $-\text{NR}_1-\text{CO}$ ,
- 5  $-\text{NR}_1-\text{CS}$ ,
- 6  $-\text{COO}-$ ,
- 7  $-\text{OCO}-$ ;
- 8  $-\text{CSO}-$ ;
- 9  $-\text{OCS}-$ ;
- 10  $-\text{CO}-\text{CR}_1=\text{CR}_1-$ ;

11  $\text{R}_2$  is hydrogen, lower alkyl of 1 to 6 carbons, F, Cl, Br, I,  $\text{CF}_3$ ,  
 12 fluoro substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6  
 13 carbons, or alkylthio of 1 to 6 carbons;

14  $\text{R}_3$  is hydrogen, lower alkyl of 1 to 6 carbons or F;

15  $m$  is an integer having the value of 0 - 3;

16  $o$  is an integer having the value of 0 - 3;

17  $\text{Y}$  is a phenyl or naphthyl group, or heteroaryl selected from a  
 18 group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl,  
 19 pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrrazolyl, said phenyl and  
 20 heteroaryl groups being optionally substituted with one or two  $\text{R}_2$   
 21 groups, or

22 when  $\text{Z}$  is  $-(\text{CR}_1=\text{CR}_1)_{n'}$ - and  $n'$  is 3, 4 or 5 then  $\text{Y}$  represents a  
 23 direct valence bond between said  $(\text{CR}_2=\text{CR}_2)_{n'}$  group and  $\text{B}$ ;

24  $\text{A}$  is  $(\text{CH}_2)_q$  where  $q$  is 0-5, lower branched chain alkyl  
 25 having 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6  
 26 carbons and 1 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2  
 27 triple bonds;

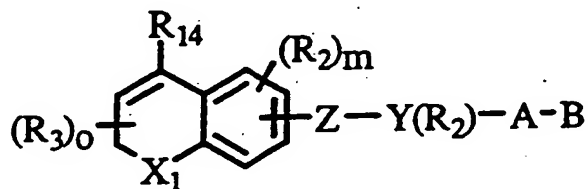
28  $\text{B}$  is hydrogen,  $\text{COOH}$  or a pharmaceutically acceptable salt

1 thereof,  $\text{COOR}_8$ ,  $\text{CONR}_9\text{R}_{10}$ ,  $-\text{CH}_2\text{OH}$ ,  $\text{CH}_2\text{OR}_{11}$ ,  $\text{CH}_2\text{OCOR}_{11}$ ,  $\text{CHO}$ ,  
 2  $\text{CH}(\text{OR}_{12})_2$ ,  $\text{CHOR}_{13}\text{O}$ ,  $-\text{COR}_7$ ,  $\text{CR}_7(\text{OR}_{12})_2$ ,  $\text{CR}_7\text{OR}_{13}\text{O}$ , or  $\text{Si}(\text{C}_{1-6}\text{alkyl})_3$ ,  
 3 where  $\text{R}_7$  is an alkyl, cycloalkyl or alkenyl group containing 1 to 5  
 4 carbons,  $\text{R}_8$  is an alkyl group of 1 to 10 carbons or (trimethylsilyl)alkyl  
 5 where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to  
 6 10 carbons, or  $\text{R}_8$  is phenyl or lower alkylphenyl,  $\text{R}_9$  and  $\text{R}_{10}$   
 7 independently are hydrogen, an alkyl group of 1 to 10 carbons, or a  
 8 cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl,  $\text{R}_{11}$  is  
 9 lower alkyl, phenyl or lower alkylphenyl,  $\text{R}_{12}$  is lower alkyl, and  $\text{R}_{13}$  is  
 10 divalent alkyl radical of 2-5 carbons;

11  $\text{X}_2$  is O, S, SO or  $\text{SO}_2$ , and

12  $\text{R}_{20}$  is  $\text{Si}(\text{C}_{1-6}\text{alkyl})_3$ ,  $\text{R}_{14}$ ,  $\text{COR}_{14}$ ,  $\text{SO}_2\text{R}_{21}$ , where  $\text{R}_{14}$  is hydrogen,  
 13 alkyl of 1 to 10 carbons, alkenyl of 2 to 10 carbons and having 1 to 3  
 14 double bond, alkynyl having 2 to 10 carbons and 1 to 3 triple bonds,  
 15 carbocyclic aryl selected from the group consisting of phenyl,  $\text{C}_1 -$   
 16  $\text{C}_{10}$ -alkylphenyl, naphthyl,  $\text{C}_1 - \text{C}_{10}$ -alkylnaphthyl, phenyl- $\text{C}_1 - \text{C}_{10}$ alkyl,  
 17 naphthyl- $\text{C}_1 - \text{C}_{10}$ alkyl, or  $\text{R}_{20}$  is hydroxyalkyl, aminoalkyl or thioalkyl  
 18 having 1 to 10 carbons; and  $\text{R}_{21}$  is alkyl of 1 to 10 carbons, fluoroalkyl of  
 19 1 to 10 carbons, or carbocyclic aryl selected from the group consisting of  
 20 phenyl,  $\text{C}_1 - \text{C}_{10}$ -alkylphenyl and phenyl- $\text{C}_1 - \text{C}_{10}$ alkyl, and

21 compounds of Formula 6



Formula 6

1            wherein  $X_1$  is  $[C(R_1)_2]_n$  where  $R_1$  is independently H or alkyl of 1  
2            to 6 carbons, and  $n$  is an integer between 0 and 2;

3             $Z$  is  $-N=N-$ ,

4                         $-N(O)=N-$ ,

5                         $-N=N(O)-$ ,

6                         $-N=CR_1-$ ,

7                         $-CR_1=N$ ,

8                         $-(CR_1=CR_1)_{n'}$  where  $n'$  is an integer having the value 0 - 5,

9                         $-CO-NR_1-$ ,

10                        $-CS-NR_1-$ ,

11                        $-NR_1-CO$ ,

12                        $-NR_1-CS$ ,

13                        $-COO-$ ,

14                        $-OCO-$ ;

15                        $-CSO-$ ;

16                        $-OCS-$ ;

17                        $-CO-CR_1=CR_1-$ ;

18             $R_2$  is hydrogen, lower alkyl of 1 to 6 carbons, F, Cl, Br, I,  $CF_3$ ,  
19            fluoro substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6  
20            carbons, or alkylthio of 1 to 6 carbons;

21             $R_3$  is hydrogen, lower alkyl of 1 to 6 carbons or F;

22             $m$  is an integer having the value of 0 - 3;

23             $o$  is an integer having the value of 0 - 3;

24             $Y$  is a phenyl or naphthyl group, or heteroaryl selected from a  
25            group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl,  
26            pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and  
27            heteroaryl groups being optionally substituted with one or two  $R_2$   
28            groups, or

1 when Z is  $-(CR_1=CR_1)_r-$  and n' is 3, 4 or 5 then Y represents a  
 2 direct valence bond between said  $(CR_2=CR_2)_r$  group and B;

3 A is  $(CH_2)_q$  where q is 0-5, lower branched chain alkyl  
 4 having 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6  
 5 carbons and 1 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2  
 6 triple bonds;

7 B is hydrogen, COOH or a pharmaceutically acceptable salt  
 8 thereof,  $COOR_9$ ,  $CONR_9R_{10}$ ,  $-CH_2OH$ ,  $CH_2OR_{11}$ ,  $CH_2OCOR_{11}$ ,  $CHO$ ,  
 9  $CH(OR_{12})_2$ ,  $CHOR_{13}O$ ,  $-COR_7$ ,  $CR_7(OR_{12})_2$ ,  $CR_7OR_{13}O$ , or  $Si(C_{1-6}alkyl)_3$ ,  
 10 where  $R_7$  is an alkyl, cycloalkyl or alkenyl group containing 1 to 5  
 11 carbons,  $R_8$  is an alkyl group of 1 to 10 carbons or (trimethylsilyl)alkyl  
 12 where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to  
 13 10 carbons, or  $R_8$  is phenyl or lower alkylphenyl,  $R_9$  and  $R_{10}$   
 14 independently are hydrogen, an alkyl group of 1 to 10 carbons, or a  
 15 cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl,  $R_{11}$  is  
 16 lower alkyl, phenyl or lower alkylphenyl,  $R_{12}$  is lower alkyl, and  $R_{13}$  is  
 17 divalent alkyl radical of 2-5 carbons; and

18  $R_{14}$  is  $(R_{15})_r$ -substituted alkyl of 1 - 6 carbons,  $(R_{15})_r$ -substituted  
 19 alkenyl of 1 - 6 carbons and 1 or 2 double bonds,  $(R_{15})_r$ -substituted  
 20 alkynyl of 1 - 6 carbons and 1 or 2 triple bonds,  $(R_{15})_r$ -phenyl,  
 21  $(R_{15})_r$ -naphthyl, or  $(R_{15})_r$ -heteroaryl where the heteroaryl group has 1 to  
 22 3 heteroatoms selected from the group consisting of O, S and N, r is an  
 23 integer having the values of 0 - 5, and

24  $R_{15}$  is independently H, F, Cl, Br, I,  $NO_2$ ,  $N(R_8)_2$ ,  $N(R_8)COR_9$ ,  
 25  $NR_8CON(R_8)_2$ , OH,  $OCOR_9$ ,  $OR_9$ , CN, COOH,  $COOR_8$  an alkyl group  
 26 having 1 to 10 carbons, fluoro substituted alkyl group having 1 to 10  
 27 carbons, an alkenyl group having 1 to 10 carbons and 1 to 3 double  
 28 bonds, alkynyl group having 1 to 10 carbons and 1 to 3 triple bonds, or



1 a (trialkyl)silyl or (trialkyl)silyloxy group where the alkyl groups  
2 independently have 1 to 6 carbons.

3 In a second aspect, this invention relates to the use of the  
4 compounds of Formula 1 through Formula 6 for the treatment of  
5 skin-related diseases, including, without limitation, actinic keratoses,  
6 arsenic keratoses, inflammatory and non-inflammatory acne, psoriasis,  
7 ichthyoses and other keratinization and hyperproliferative disorders of  
8 the skin, eczema, atopic dermatitis, Darriers disease, lichen planus,  
9 prevention and reversal of glucocorticoid damage (steroid atrophy), as a  
10 topical anti-microbial, as skin anti-pigmentation agents and to treat and  
11 reverse the effects of age and photo damage to the skin. The  
12 compounds are also useful for the prevention and treatment of  
13 cancerous and precancerous conditions, including, premalignant and  
14 malignant hyperproliferative diseases such as cancers of the breast, skin,  
15 prostate, cervix, uterus, colon, bladder, esophagus, stomach, lung, larynx,  
16 oral cavity, blood and lymphatic system, metaplasias, dysplasias,  
17 neoplasias, leukoplakias and papillomas of the mucous membranes and  
18 in the treatment of Kaposi's sarcoma. In addition, the present  
19 compounds can be used as agents to treat diseases of the eye, including,  
20 without limitation, proliferative vitreoretinopathy (PVR), retinal  
21 detachment, dry eye and other corneopathies, as well as in the  
22 treatment and prevention of various cardiovascular diseases, including,  
23 without limitation, diseases associated with lipid metabolism such as  
24 dyslipidemias, prevention of post-angioplasty restenosis and as an agent  
25 to increase the level of circulating tissue plasminogen activator (TPA).  
26 Other uses for the compounds of the present invention include the  
27 prevention and treatment of conditions and diseases associated with  
28 Human papilloma virus (HPV), including warts and genital warts,

1 various inflammatory diseases such as pulmonary fibrosis, ileitis, colitis  
2 and Krohn's disease, neurodegenerative diseases such as Alzheimer's  
3 disease, Parkinson's disease and stroke, improper pituitary function,  
4 including insufficient production of growth hormone, modulation of  
5 apoptosis, including both the induction of apoptosis and inhibition of  
6 T-Cell activated apoptosis, restoration of hair growth, including  
7 combination therapies with the present compounds and other agents  
8 such as Minoxidil<sup>R</sup>, diseases associated with the immune system,  
9 including use of the present compounds as immunosuppressants and  
10 immunostimulants, modulation of organ transplant rejection and  
11 facilitation of wound healing, including modulation of chelosis.

12 Alternatively, those compounds of the invention which act as  
13 antagonists of one or more retinoid receptor subtypes are useful to  
14 prevent certain undesired side effects of retinoids which are  
15 administered for the treatment or prevention of certain diseases or  
16 conditions. For this purpose the retinoid antagonist compounds of the  
17 invention may be co-administered with retinoids. The compounds of  
18 the present invention are also useful in the treatment of acute or  
19 chronic toxicity resulting from overdose or poisoning by retinoid drugs  
20 or Vitamin A.

21 This invention also relates to a pharmaceutical formulation  
22 comprising a compound of Formula 1 through Formula 6 in admixture  
23 with a pharmaceutically acceptable excipient, said formulation being  
24 adapted for administration to a mammal, including a human being, to  
25 treat or alleviate the conditions which were described above as treatable  
26 by retinoids, to be co-administered with retinoids to eliminate or  
27 reduce side effects of retinoids, or to treat retinoid or Vitamin A  
28 overdose or poisoning.

## BIOLOGICAL ACTIVITY, MODES OF ADMINISTRATION

### Assay of Retinoid-like or Retinoid Antagonist-like Biological Activity

A classic measure of retinoic acid activity involves measuring the effects of retinoic acid on ornithine decarboxylase. The original work on the correlation between retinoic acid and decrease in cell proliferation was done by Verma & Boutwell, Cancer Research, 1977, 37,2196-2201. That reference discloses that ornithine decarboxylase (ODC) activity increased precedent to polyamine biosynthesis. It has been established elsewhere that increases in polyamine synthesis can be correlated or associated with cellular proliferation. Thus, if ODC activity could be inhibited, cell hyperproliferation could be modulated. Although all cases for ODC activity increases are unknown, it is known that 12-0-tetradecanoylphorbol-13-acetate (TPA) induces ODC activity. Retinoic acid inhibits this induction of ODC activity by TPA. An assay essentially following the procedure set out in Cancer Research: 1662-1670, 1975 may be used to demonstrate inhibition of TPA induction of ODC by compounds of this invention. Activity of exemplary compounds of the present invention in the above-described ODC assay is disclosed in Table 1 which provides the  $IC_{60}$  concentration for the respective exemplary compound. (" $IC_{60}$ " is that concentration of the test compound which causes 60% inhibition in the ODC assay. By analogy, " $IC_{80}$ ", for example, is that concentration of the test compound which causes 80% inhibition in the ODC assay.)

**TABLE 1**  
**ODC Assay**

Compound N .	IC <sub>50</sub> (nmols)
A5	10.3
D3	8.4
C22b	10
E24	8.3
A16	4.3 (IC <sub>80</sub> )
C14	4
E79	5.3
D34	4.3 (IC <sub>80</sub> )
C15	14.5
E15	24.7
A27	0.7
E16	88.4
A23	43.7
A2	27
E72b	18
E56a	3.1
D6	1.9

Other assays described below, measure the ability of the compounds of the present invention to bind to, and/or activate various retinoid receptor subtypes. When in these assays a compound binds to a given receptor subtype and activates the transcription of a reporter gene through that subtype, then the compound is considered an agonist of that receptor subtype. Conversely, a compound is considered an antagonist of a given receptor subtype if in the below described co-transfection assays the compound does not cause significant transcriptional activation of the receptor regulated reporter gene, but nevertheless binds to the receptor with a K<sub>d</sub> value of less than approximately 1 micromolar. In the below described assays the ability of the compounds to bind to RAR<sub>α</sub>, RAR<sub>β</sub>, RAR<sub>γ</sub>, RXR<sub>α</sub>, RXR<sub>β</sub> and

1 RXR<sub>γ</sub> receptors, and the ability or inability of the compounds to  
2 activate transcription of a reporter gene through these receptor subtypes  
3 can be tested.

4 Specifically, a **chimeric receptor transactivation assay** which tests  
5 for agonist-like activity in the RAR<sub>α</sub>, RAR<sub>β</sub>, RAR<sub>γ</sub>, RXR<sub>α</sub> receptor  
6 subtypes, and which is based on work published by Feigner P. L. and  
7 Holm M. (1989) Focus, 11 2 is described in detail in United States  
8 Patent No. 5,455,265 the specification of which is hereby expressly  
9 incorporated by reference.

10 A **holoreceptor transactivation assay** and a **ligand binding assay**  
11 which measure the antagonist/agonist like activity of the compounds of  
12 the invention, or their ability to bind to the several retinoid receptor  
13 subtypes, respectively, are described in published PCT Application No.  
14 WO WO93/11755 (particularly on pages 30 - 33 and 37 - 41) published  
15 on June 24, 1993, the specification of which is also incorporated herein  
16 by reference. A description of the **holoreceptor transactivation assay** is  
17 also provided below.

#### 18 **HOLORECEPTOR TRANSACTIVATION ASSAY**

19 CV1 cells (5,000 cells/well) were transfected with an RAR  
20 reporter plasmid MTV-TREp-LUC (50 ng) along with one of the RAR  
21 expression vectors (10 ng) in an automated 96-well format by the  
22 calcium phosphate procedure of Heyman et al. Cell 68, 397 - 406,  
23 (1992). For RXR<sub>α</sub> and RXR<sub>γ</sub> transactivation assays, an  
24 RXR-responsive reporter plasmid CRBP<sub>II</sub>-tk-LUC (50 ng) along with  
25 the appropriate RXR expression vectors (10 ng) was used substantially  
26 as described by Heyman et al. above, and Allegretto et al. J. Biol.  
27 Chem. 268, 26625 - 26633. For RXR<sub>β</sub> transactivation assays, an  
28 RXR-responsive reporter plasmid CPRE-tk-LUC (50 mg) along with

1 RXR<sub>β</sub> expression vector (10 mg) was used as described in above. These  
2 reporters contain DRI elements from human CRBP<sub>II</sub> and certain DRI  
3 elements from promoter, respectively. (see Mangelsdorf et al. The  
4 Retinoids: Biology, Chemistry and Medicine, pp 319 - 349, Raven Press  
5 Ltd., New York and Heyman et al., cited above) (1, 8). A  
6 β-galactosidase (50 ng) expression vector was used as an internal control  
7 in the transfections to normalize for variations in transfection efficiency.  
8 The cells were transfected in triplicate for 6 hours, followed by  
9 incubation with retinoids for 36 hours, and the extracts were assayed for  
10 luciferase and β-galactosidase activities. The detailed experimental  
11 procedure for holoreceptor transactivations has been described in  
12 Heyman et al. above, and Allegretto et al. cited above. The results  
13 obtained in this assay are expressed in EC<sub>50</sub> numbers, as they are also  
14 in the chimeric receptor transactivation assay. The Heyman et al. Cell  
15 68, 397 - 406, Allegretto et al. J. Biol. Chem. 268, 26625 - 26633, and  
16 Mangelsdorf et al. The Retinoids: Biology, Chemistry and Medicine, pp  
17 319 - 349, Raven Press Ltd., New York, are expressly incorporated  
18 herein by reference. The results of ligand binding assay are expressed  
19 in K<sub>d</sub> numbers. (See Cheng et al. Biochemical Pharmacology Vol. 22 pp  
20 3099-3108, expressly incorporated herein by reference.)

21 Table 2 shows the results of the ligand binding assay for certain  
22 exemplary compounds of the invention for the receptor subtypes in the  
23 RAR group.

**TABLE 2**  
**Ligand Binding Assay**

Compound No.	K <sub>d</sub> (nanomolar, nM)		
	RAR $\alpha$	RAR $\beta$	RAR $\gamma$
A6	125	36	127
D4	1000	132	363
C25	19	12	42
E27	551	535	>1000
A18	538	193	162
E80	394	531	901
D34	235	200	530
E14	36	35	455
A28	4	3	42
E17	192	378	>1000
A24	283	92	259
A2a	150	219	421
E67	77	302	375
D7	>1000	226	>1000

#### Modes of Administration

The compounds of this invention may be administered systemically or topically, depending on such considerations as the condition to be treated, need for site-specific treatment, quantity of drug to be administered, and numerous other considerations.

In the treatment of dermatoses, it will generally be preferred to administer the drug topically, though in certain cases such as treatment of severe cystic acne or psoriasis, oral administration may also be used. Any common topical formulation such as a solution, suspension, gel, ointment, or salve and the like may be used. Preparation of such topical formulations are well described in the art of pharmaceutical formulations as exemplified, for example, by Remington's

1    Pharmaceutical Science, Edition 17, Mack Publishing Company, Easton,  
2    Pennsylvania. For topical application, these compounds could also be  
3    administered as a powder or spray, particularly in aerosol form. If the  
4    drug is to be administered systemically, it may be conected as a  
5    powder, pill, tablet or the like or as a syrup or elixir suitable for oral  
6    administration. For intravenous or intraperitoneal administration, the  
7    compound will be prepared as a solution or suspension capable of being  
8    administered by injection. In certain cases, it may be useful to  
9    formulate these compounds by injection. In certain cases, it may be  
10   useful to formulate these compounds in suppository form or as extended  
11   release formulation for deposit under the skin or intramuscular  
12   injection.

13       Other medicaments can be added to such topical formulation for  
14   such secondary purposes as treating skin dryness; providing protection  
15   against light; other medications for treating dermatoses; medicaments  
16   for preventing infection, reducing irritation, inflammation and the like.

17       Treatment of dermatoses or any other indications known or  
18   discovered to be susceptible to treatment by retinoic acid-like  
19   compounds will be effected by administration of the therapeutically  
20   effective dose of one or more compounds of the instant invention. A  
21   therapeutic concentration will be that concentration which effects  
22   reduction of the particular condition, or retards it expansion. In certain  
23   instances, the compound potentially may be used in prophylactic  
24   manner to prevent onset of a particular condition.

25       A useful therapeutic or prophylactic concentration will vary from  
26   condition to condition and in certain instances may vary with the  
27   severity of the condition being treated and the patient's susceptibility to  
28   treatment. Accordingly, no single concentration will be uniformly



1 useful, but will require modification depending on the particularities of  
2 the disease being treated. Such concentrations can be arrived at  
3 through routine experimentation. However, it is anticipated that in the  
4 treatment of, for example, acne, or similar dermatoses, that a  
5 formulation containing between 0.01 and 1.0 milligrams per milliliter of  
6 formulation will constitute a therapeutically effective concentration for  
7 total application. If administered systemically, an amount between 0.01  
8 and 5 mg per kg per day of body weight would be expected to effect a  
9 therapeutic result in the treatment of many diseases for which these  
10 compounds are useful.

11 Those partial or pan retinoid antagonist compounds of the  
12 invention, when used to take advantage of their antagonist property, can  
13 be co-administered to mammals, including humans, with retinoid  
14 agonists and, by means of pharmacological selectivity or site-specific  
15 delivery, preferentially prevent the undesired effects of certain retinoid  
16 agonists. The antagonist compounds of the invention can also be used  
17 to treat Vitamin A overdose, acute or chronic, resulting either from the  
18 excessive intake of vitamin A supplements or from the ingestion of liver  
19 of certain fish and animals that contain high levels of Vitamin A. Still  
20 further, the antagonist compounds of the invention can also be used to  
21 treat acute or chronic toxicity caused by retinoid drugs. It has been  
22 known in the art that the toxicities observed with hypervitaminosis A  
23 syndrome (headache, skin peeling, bone toxicity, dyslipidemias) are  
24 similar or identical with toxicities observed with other retinoids,  
25 suggesting a common biological cause, that is RAR activation. Because  
26 the antagonist compounds of the present invention block RAR  
27 activation, they are suitable for treating the foregoing toxicities.

28 Generally speaking, for therapeutic applications in mammals, the

1 antagonist compounds of the invention can be administered enterally or  
2 topically as an antidote to vitamin A, or antidote to retinoid toxicity  
3 resulting from overdose or prolonged exposure, after intake of the  
4 causative factor (vitamin A, vitamin A precursor, or other retinoid) has  
5 been discontinued. Alternatively, the antagonist compounds of the  
6 invention are co-administered with retinoid drugs, in situations where  
7 the retinoid provides a therapeutic benefit, and where the  
8 co-administered antagonist compound alleviates or eliminates one or  
9 more undesired side effects of the retinoid. For this type of application  
10 the antagonist compound may be administered in a site-specific manner,  
11 for example as a topically applied cream or lotion while the  
12 co-administered retinoid may be given enterally. For therapeutic  
13 applications the antagonist compounds of the invention, like the retinoid  
14 agonists compounds, are incorporated into pharmaceutical  
15 compositions, such as tablets, pills, capsules, solutions, suspensions,  
16 creams, ointments, gels, salves, lotions and the like, using such  
17 pharmaceutically acceptable excipients and vehicles which per se are  
18 well known in the art. For topical application, the antagonist  
19 compounds of the invention could also be administered as a powder or  
20 spray, particularly in aerosol form. If the drug is to be administered  
21 systemically, it may be confected as a powder, pill, tablet or the like or  
22 as a syrup or elixir suitable for oral administration. For intravenous or  
23 intraperitoneal administration, the compound will be prepared as a  
24 solution or suspension capable of being administered by injection. In  
25 certain cases, it may be useful to formulate these compounds by  
26 injection. In certain cases, it may be useful to formulate these  
27 compounds in suppository form or as extended release formulation for  
28 deposit under the skin or intramuscular injection.

1       The antagonist compounds also, like the retinoid agonists of the  
2 invention, will be administered in a therapeutically effective dose. A  
3 therapeutic concentration will be that concentration which effects  
4 reduction of the particular condition, or retards its expansion. When  
5 co-administering the compounds of the invention to block  
6 retinoid-induced toxicity or side effects, the antagonist compounds of  
7 the invention are used in a prophylactic manner to prevent onset of a  
8 particular condition, such as skin irritation.

9       A useful therapeutic or prophylactic concentration will vary from  
10 condition to condition and in certain instances may vary with the  
11 severity of the condition being treated and the patient's susceptibility to  
12 treatment. Accordingly, no single concentration will be uniformly  
13 useful, but will require modification depending on the particularities of  
14 the chronic or acute retinoid toxicity or related condition being treated.  
15 Such concentrations can be arrived at through routine experimentation.  
16 However, it is anticipated that a formulation containing between 0.01  
17 and 1.0 milligrams per milliliter of formulation will constitute a  
18 therapeutically effective concentration for total application. If  
19 administered systemically, an amount between 0.01 and 5 mg per kg per  
20 day of body weight would be expected to effect a therapeutic result.

## 1      **GENERAL EMBODIMENTS AND SYNTHETIC METHODOLOGY**

### 2      **Definitions**

3            The term alkyl refers to and covers any and all groups which are  
4      known as normal alkyl, branched-chain alkyl and cycloalkyl. The term  
5      alkenyl refers to and covers normal alkenyl, branch chain alkenyl and  
6      cycloalkenyl groups having one or more sites of unsaturation. Similarly,  
7      the term alkynyl refers to and covers normal alkynyl, and branch chain  
8      alkynyl groups having one or more triple bonds.

9            Lower alkyl means the above-defined broad definition of alkyl  
10     groups having 1 to 6 carbons in case of normal lower alkyl, and as  
11     applicable 3 to 6 carbons for lower branch chained and cycloalkyl  
12     groups. Lower alkenyl is defined similarly having 2 to 6 carbons for  
13     normal lower alkenyl groups, and 3 to 6 carbons for branch chained and  
14     cyclo- lower alkenyl groups. Lower alkynyl is also defined similarly,  
15     having 2 to 6 carbons for normal lower alkynyl groups, and 4 to 6  
16     carbons for branch chained lower alkynyl groups.

17           The term "ester" as used here refers to and covers any compound  
18     falling within the definition of that term as classically used in organic  
19     chemistry. It includes organic and inorganic esters. Where B (of  
20     Formula 1 through 6) is  $\text{-COOH}$ , this term covers the products derived  
21     from treatment of this function with alcohols or thiols preferably with  
22     aliphatic alcohols having 1-6 carbons. Where the ester is derived from  
23     compounds where B is  $\text{-CH}_2\text{OH}$ , this term covers compounds derived  
24     from organic acids capable of forming esters including phosphorous  
25     based and sulfur based acids, or compounds of the formula  
26      $\text{-CH}_2\text{OCOR}_{11}$  where  $\text{R}_{11}$  is any substituted or unsubstituted aliphatic,  
27     aromatic, heteroaromatic or aliphatic aromatic group, preferably with  
28     1-6 carbons in the aliphatic portions.

1 Unless stated otherwise in this application, preferred esters are  
2 derived from the saturated aliphatic alcohols or acids of ten or fewer  
3 carbon atoms or the cyclic or saturated aliphatic cyclic alcohols and  
4 acids of 5 to 10 carbon atoms. Particularly preferred aliphatic esters are  
5 those derived from lower alkyl acids and alcohols. Also preferred are  
6 the phenyl or lower alkyl phenyl esters.

7 Amides has the meaning classically accorded that term in organic  
8 chemistry. In this instance it includes the unsubstituted amides and all  
9 aliphatic and aromatic mono- and di- substituted amides. Unless stated  
10 otherwise in this application, preferred amides are the mono- and  
11 di-substituted amides derived from the saturated aliphatic radicals of ten  
12 or fewer carbon atoms or the cyclic or saturated aliphatic-cyclic radicals  
13 of 5 to 10 carbon atoms. Particularly preferred amides are those  
14 derived from substituted and unsubstituted lower alkyl amines. Also  
15 preferred are mono- and disubstituted amides derived from the  
16 substituted and unsubstituted phenyl or lower alkylphenyl amines.  
17 Unsubstituted amides are also preferred.

18 Acetals and ketals include the radicals of the formula-CK where  
19 K is  $(-OR)_2$ . Here, R is lower alkyl. Also, K may be  $-OR, O-$  where R,  
20 is lower alkyl of 2-5 carbon atoms, straight chain or branched.

21 A pharmaceutically acceptable salt may be prepared for any  
22 compounds in this invention having a functionality capable of forming a  
23 salt, for example an acid functionality. A pharmaceutically acceptable  
24 salt is any salt which retains the activity of the parent compound and  
25 does not impart any deleterious or untoward effect on the subject to  
26 which it is administered and in the context in which it is administered.

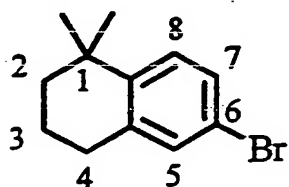
27 Pharmaceutically acceptable salts may be derived from organic or  
28 inorganic bases. The salt may be a mono or polyvalent ion. Of

1 particular interest are the inorganic ions, sodium, potassium, calcium,  
2 and magnesium. Organic salts may be made with amines, particularly  
3 ammonium salts such as mono-, di- and trialkyl amines or ethanol  
4 amines. Salts may also be formed with caffeine, tromethamine and  
5 similar molecules. Where there is a nitrogen sufficiently basic as to be  
6 capable of forming acid addition salts, such may be formed with any  
7 inorganic or organic acids or alkylating agent such as methyl iodide.  
8 Preferred salts are those formed with inorganic acids such as  
9 hydrochloric acid, sulfuric acid or phosphoric acid. Any of a number of  
10 simple organic acids such as mono-, di- or tri- acid may also be used.

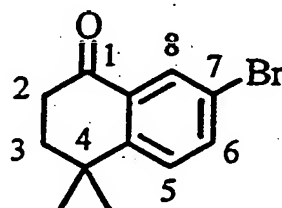
11 Some of the compounds of the present invention may have *trans*  
12 and *cis* (E and Z) isomers. In addition, the compounds of the present  
13 invention may contain one or more chiral centers and therefore may  
14 exist in enantiomeric and diastereomeric forms. Still further oxime and  
15 related compounds of the present invention may exist in *syn* and *anti*  
16 isomeric forms. The scope of the present invention is intended to cover  
17 all such isomers *per se*, as well as mixtures of *cis* and *trans* isomers,  
18 mixtures of *syn* and *anti* isomers, mixtures of diastereomers and racemic  
19 mixtures of enantiomers (optical isomers) as well. In the present  
20 application when no specific mention is made of the configuration (*cis*,  
21 *trans*, *syn* or *anti* or R or S) of a compound (or of an asymmetric  
22 carbon) then a mixture of such isomers, or either one of the isomers is  
23 intended. In a similar vein, when in the chemical structural formulas of  
24 this application a straight line representing a valence bond is drawn to  
25 an asymmetric carbon, then isomers of both R and S configuration, as  
26 well as their mixtures are intended. Defined stereochemistry about an  
27 asymmetric carbon is indicated in the formulas (where applicable) by a  
28 solid triangle showing  $\beta$  configuration, or by a hashed line showing  $\alpha$

1 configuration.

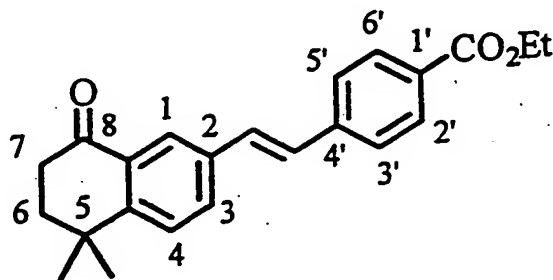
2 Referring now to the nomenclature used in naming the  
3 compounds of the invention and intermediate compounds leading  
4 thereto, the system for numbering the tetrahydronaphthalene ring is  
5 demonstrated as shown by the structural formulas of Compounds F, G  
6 and A2. Compound A2 is an exemplary compound of the invention  
7 within the scope of Formula 2 and Compounds F and G are two  
8 exemplary intermediates utilized in the synthesis of the compounds of  
9 the invention. The numbering systems illustrated here corresponds  
10 substantially to IUPAC rules, and will be readily apparent to those  
11 skilled in the art as it is applied in the ensuing description.



20 Compound F



Compound G



Compound A2

1           Generally speaking, the compounds of the invention are made in  
 2   synthetic steps which involve the formation of the  
 3   tetrahydronaphthalene, dihydronaphthalene, indane or suberane  
 4   moiety, substituted with the desired  $R_1$ ,  $R_2$  and  $R_3$  groups and with a  
 5   reactive group, such as bromo group, that allows coupling with a reagent  
 6   that introduces the  $-Z-Y(R_2)-A-B$  group. Such a reagent can be  
 7   generally described as  $X_3-Z-Y(R_2)-A-B$

8   where  $X_3$  is a reactive group, in many instances a leaving group, such as  
 9   halogen. The  $-Z-Y(R_2)-A-B$  group may also be formed in a series of  
 10   reactions performed starting with the tetrahydronaphthalene,  
 11   dihydronaphthalene, indane or suberane molecule that has the  
 12   appropriate reactive group or reactive position. in the aromatic nucleus.

13           The substituent or substituents in the 5 or 8 positions of the  
 14   tetrahydronaphthalene or dihydronaphthalene (and by analogy in the  
 15   corresponding positions of indane and suberan) which are designated as  
 16    $R_4$  and  $X_2R_5$  in Formula 1, as  $(X_2R_{18})_2$  in Formula 2,  $=C(R_{19})_2$  in  
 17   Formula 3,  $N=Z_2$  in Formula 4,  $X_2R_{20}$  in Formula 5 and  $R_{14}$  in Formula  
 18   6 may be introduced into the tetrahydronaphthalene or  
 19   dihydronaphthalene ring moiety before coupling with the reagent  $X_3-Z-$   
 20    $Y(R_2)-A-B$ , or before formation of the  $-Z-Y(R_2)-A-B$  group. In other  
 21   examples coupling with the reagent  $X_3-Z-Y(R_2)-A-B$  or formation of  
 22   the  $-Z-Y(R_2)-A-B$  group attached to the tetrahydronaphthalene or  
 23   dihydronaphthalene nucleus is performed first to yield an intermediate  
 24   that includes the tetrahydronaphthalene, dihydronaphthalene (and by  
 25   analogy indane or suberane) moiety covalently linked to the  $-Z-Y(R_2)-A-$   
 26   B group, but which has a reactive group, preferably such as an oxo or  
 27   trifluoromethanesulfonyloxy function, in the 5 or 8 position. In these  
 28   cases the substituents of these two positions, as defined in Formulas 1 -



1 6, are introduced into the intermediate by appropriate reactions which  
2 are described in detail below.

3 The synthetic methodology employed for the synthesis of the  
4 compounds of the present invention may also include transformations of  
5 the group designated as -A-B in Formulas 1 - 6. Generally speaking  
6 these transformations involve reactions well within the skill of the  
7 practicing organic chemist. In this regard the following well known and  
8 published general principles and synthetic methodology are briefly  
9 described.

10 Carboxylic acids are typically esterified by refluxing the acid in a  
11 solution of the appropriate alcohol in the presence of an acid catalyst  
12 such as hydrogen chloride or thionyl chloride. Alternatively, the  
13 carboxylic acid can be condensed with the appropriate alcohol in the  
14 presence of dicyclohexylcarbodiimide and dimethylaminopyridine. The  
15 ester is recovered and purified by conventional means. Acetals and  
16 ketals are readily made by the method described in March, "Advanced  
17 Organic Chemistry," 2nd Edition, McGraw-Hill Book Company, p 810).  
18 Alcohols, aldehydes and ketones all may be protected by forming  
19 respectively, ethers and esters, acetals or ketals by known methods such  
20 as those described in McOmie, Plenum Publishing Press, 1973 and  
21 Protecting Groups, Ed. Greene, John Wiley & Sons, 1981.

22 To increase the value of n in the compounds of  $X_3-Z-Y(R_2)-A-B$   
23 or precursors thereof, before affecting the coupling or linkage with the  
24 tetrahydronaphthalene, dihydronaphthalene nucleus (where such  
25 compounds are not available from a commercial source) aromatic or  
26 heteroaromatic carboxylic acids are subjected to homologation by  
27 successive treatment under Arndt-Eistert conditions or other  
28 homologation procedures. Alternatively, derivatives which are not

1 carboxylic acids may also be homologated by appropriate procedures.  
2 The homologated acids can then be esterified by the general procedure  
3 outlined in the preceding paragraph.

4 Compounds of formula  $X_3-Z-Y(R_2)-A-B$  (or of the invention  
5 as set forth in Formulas 1 through 6, as applicable) where A is an  
6 alkenyl group having one or more double bonds can be made for  
7 example, by synthetic schemes well known to the practicing organic  
8 chemist; for example by Wittig and like reactions, or by introduction of  
9 a double bond by elimination of halogen from an  
10 alpha-halo-arylalkyl-carboxylic acid, ester or like carboxaldehyde.

11 Compounds of formula  $X_3-Z-Y(R_2)-A-B$  (or of the invention as set  
12 forth in Formulas 1 through 6, as applicable) where the A group has a  
13 triple (acetylenic) bond can be made by reaction of a corresponding  
14 aromatic methyl ketone with strong base, such as lithium diisopropyl  
15 amide, reaction with diethyl chlorophosphate and subsequent addition  
16 of lithium diisopropylamide.

17 The acids and salts derived from compounds of the invention are  
18 readily obtainable from the corresponding esters. Basic saponification  
19 with an alkali metal base will provide the acid. For example, an ester of  
20 the invention may be dissolved in a polar solvent such as an alkanol,  
21 preferably under an inert atmosphere at room temperature, with about  
22 a three molar excess of base, for example, lithium hydroxide or  
23 potassium hydroxide. The solution is stirred for an extended period of  
24 time, between 15 and 20 hours, cooled, acidified and the hydrolysate  
25 recovered by conventional means.

26 The amide may be formed by any appropriate amidation means  
27 known in the art from the corresponding esters or carboxylic acids. One  
28 way to prepare such compounds is to convert an acid to an acid chloride

1 and then treat that compound with ammonium hydroxide or an  
2 appropriate amine. For example, the ester is treated with an alcoholic  
3 base solution such as ethanolic KOH (in approximately a 10% molar  
4 excess) at room temperature for about 30 minutes. The solvent is  
5 removed and the residue taken up in an organic solvent such as diethyl  
6 ether, treated with a dialkyl formamide and then a 10-fold excess of  
7 oxalyl chloride. This is all effected at a moderately reduced  
8 temperature between about -10 degrees and +10 degrees C. The last  
9 mentioned solution is then stirred at the reduced temperature for 1-4  
10 hours, preferably 2 hours. Solvent removal provides a residue which is  
11 taken up in an inert organic solvent such as benzene, cooled to about 0  
12 degrees C and treated with concentrated ammonium hydroxide. The  
13 resulting mixture is stirred at a reduced temperature for 1 - 4 hours.  
14 The product is recovered by conventional means.

15 Alcohols are made by converting the corresponding acids to the  
16 acid chloride with thionyl chloride or other means (J. March, "Advanced  
17 Organic Chemistry", 2nd Edition, McGraw-Hill Book Company), then  
18 reducing the acid chloride with sodium borohydride (March, Ibid, pg.  
19 1124), which gives the corresponding alcohols. Alternatively, esters may  
20 be reduced with lithium aluminum hydride at reduced temperatures.  
21 Alkylating these alcohols with appropriate alkyl halides under  
22 Williamson reaction conditions (March, Ibid, pg. 357) gives the  
23 corresponding ethers. These alcohols can be converted to esters by  
24 reacting them with appropriate acids in the presence of acid catalysts or  
25 dicyclohexylcarbodiimide and dimethylaminopyridine.

26 Aldehydes can be prepared from the corresponding primary  
27 alcohols using mild oxidizing agents such as pyridinium dichromate in  
28 methylene chloride (Corey, E. J., Schmidt, G., Tet. Lett., 399, 1979), or

1 dimethyl sulfoxide/oxalyl chloride in methylene chloride (Omura, K.,  
2 Swern, D., Tetrahedron, 1978, 34, 1651).

3 Ketones can be prepared from an appropriate aldehyde by  
4 treating the aldehyde with an alkyl Grignard reagent or similar reagent  
5 followed by oxidation.

6 Acetals or ketals can be prepared from the corresponding  
7 aldehyde or ketone by the method described in March, Ibid, p 810.

8 Reagents of formula  $X_3-Z-Y(R_2)-A-B$  (or compounds of the  
9 invention as set forth in Formulas 1 through 6, as applicable) where B is  
10 H can be prepared from the corresponding halogenated aromatic or  
11 heteroaromatic compounds, preferably where the halogen is I.

## 12 SPECIFIC EMBODIMENTS

13 With reference to the symbol Y in Formulas 1 through 6, the  
14 preferred compounds of the invention are those where Y is phenyl,  
15 naphthyl, pyridyl, thienyl or furyl. Even more preferred are compounds  
16 where Y is phenyl, naphthyl or pyridyl. As far as substitutions on the  
17 Y (phenyl), Y (pyridyl) and (Y) naphthyl groups are concerned,  
18 compounds are preferred where the phenyl group is 1,4 (para)  
19 substituted, the naphthyl group is 2,6 substituted and where the pyridine  
20 ring is 2,5 substituted. (Substitution in the 2,5 positions in the "pyridine"  
21 nomenclature corresponds to substitution in the 6-position in the  
22 "nicotinic acid" nomenclature.) In the preferred compounds of the  
23 invention there is no optional  $R_2$  substituent on the Y group.

24 The A-B group of the preferred compounds is  $(CH_2)_n-COOH$  or  
25  $(CH_2)_n-COOR_g$ , where  $R_g$  is defined as above. Even more preferably n  
26 is zero and  $R_g$  is lower alkyl.

27 Referring still to the preferred compounds of Formulas 1 through  
28 6, the  $X_1$  group is preferably  $C(R_1)_2$ , that is the preferred compounds

1 are tetrahydronaphthalene or dihydronaphthalene derivatives. The  
 2 aromatic portion of the tetrahydronaphthalene or dihydronaphthalene  
 3 moiety is preferably substituted only by the  $-Z-Y(R_2)-A-B$  group. In  
 4 other words, in the preferred compounds there is no  $R_2$  substituent  
 5 (other than hydrogen). Similarly, in the preferred compounds of the  
 6 invention there is no  $R_3$  substituent (other than hydrogen). The  $R_1$   
 7 substituent of the compounds of the invention is preferably lower alkyl,  
 8 and even more preferably methyl.

9 Preferred Z groups are:

10  $-(CR_1=CR_1)_{n'}$ - where  $n'$  is 0, 1, or 3 (when  $n'$  is 3 then Y  
 11 represents a direct valence bond between the  $-(CR_1=CR_1)_{n'}$ - group and  
 12 the  $-A-B$  group),

13  $-N=N-$ ,

14  $-CO-CR_1=CR_1-$ ,

15  $-COO-$ , and

16  $-CONH-$ .

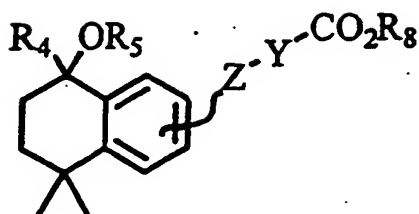
17 Referring now specifically to compounds in accordance with  
 18 Formula 1, compounds in these series are preferred where  $X_2$  is O, the  
 19  $R_4$  group is H, lower alkyl, or  $CH_2COOR_8$ , and  $R_5$  is H,  $Si(C_{1-6}alkyl)_3$ ,  
 20  $COR_{14}$ ,  $C(R_{15})(R_{16})X_2R_{17}$ ,  $COCH_3$  for  $COR_{14}$ , and  $CH_2OCH_3$  and 2-(1-  
 21 tetrahydropyranyl) for the  $C(R_{15})(R_{16})X_2R_{17}$  group are particularly  
 22 preferred.

23 The most preferred compounds in accordance with Formula 1 are  
 24 listed below in the Table for Formula 1A and with reference to that  
 25 formula.

26

27

28



Formula 1A

TABLE For Formula 1A

Compound No.	R <sub>4</sub>	R <sub>5</sub>	Z	Y	R <sub>8</sub>	Configuration, When Applicable and or position of substituent Z
A-32	CH <sub>2</sub> COOEt	H	CH=CH	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	Et	2
B-3	H	t-butyl dimethyl silyl	---	2,6-C <sub>10</sub> H <sub>8</sub> <sup>2</sup>	Et	2
B-4	H	H	---	2,6-C <sub>10</sub> H <sub>8</sub> <sup>2</sup>	Et	2
B-5	H	H	---	2,6-C <sub>10</sub> H <sub>8</sub> <sup>2</sup>	H	2
B-8	H	CH <sub>2</sub> OCH <sub>3</sub>	---	2,6-C <sub>10</sub> H <sub>8</sub> <sup>2</sup>	Et	2
B-9	H	CH <sub>2</sub> OCH <sub>3</sub>	---	2,6-C <sub>10</sub> H <sub>8</sub> <sup>2</sup>	H	2
B-10	H	COCH <sub>3</sub>	---	2,6-C <sub>10</sub> H <sub>8</sub> <sup>2</sup>	Et	2
C-13	H	H	polyene <sup>4</sup>	---	Et	2
C-19	H	H	polyene <sup>4</sup>	---	H	2
C-26	H	CH <sub>2</sub> OCH <sub>3</sub>	polyene <sup>4</sup>	---	Et	2
C-27	H	CH <sub>2</sub> OCH <sub>3</sub>	polyene <sup>4</sup>	---	H	2
C-29	H	THP <sup>3</sup>	polyene <sup>4</sup>	---	Et	2
C-31	H	THP <sup>3</sup>	polyene <sup>4</sup>	---	H	2
D-1	CH <sub>2</sub> COOEt	H	-N=N-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	Et	2
D-5	H	H	-N=N-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	Et	2
D-6	H	CH <sub>2</sub> OCH <sub>3</sub>	-N=N-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	Et	2
D-7	H	CH <sub>2</sub> OCH <sub>3</sub>	-N=N	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	H	2
D-27	H	CH <sub>2</sub> OCH <sub>3</sub>	CO-CH=CH-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	H	3
E-32	H	H	CO-NH	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	Et	2
E-33	H	H	-CO-NH-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	H	2
E-34	H	CH <sub>2</sub> OCH <sub>3</sub>	-CO-NH-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	Et	2

1	E-35	H	CH <sub>2</sub> OCH <sub>3</sub>	-CO-NH	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	H	2
2	E-37	H	H	-CO-O-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	(CH <sub>2</sub> ) <sub>2</sub> Si(CH <sub>3</sub> ) <sub>2</sub>	2
3	E-38	H	CH <sub>2</sub> OCH <sub>3</sub>	-CO-O-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	(CH <sub>2</sub> ) <sub>2</sub> Si(CH <sub>3</sub> ) <sub>2</sub>	2
4	E-39	H	CH <sub>2</sub> OCH <sub>3</sub>	-CO-O-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	H	2
5	E-40	H	H	-CO-O-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	Et	2
6	E-41	H	CH <sub>2</sub> OCH <sub>3</sub>	-CO-O-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	Et	2
7	E-49	CH <sub>2</sub> COOEt	COCH <sub>3</sub>	-CO-NH-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	Et	2
8	E-54	CH <sub>2</sub> COOEt	H	-CO-O-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	Et	2
9	E-56	H	THP <sup>3</sup>	-CO-O-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	Et	2
10	E-60	H	THP <sup>3</sup>	-CO-O-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	Benzyl	2
11	E-64	H	THP <sup>3</sup>	-CO-O-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	H	2
12	E-65	H	THP <sup>3</sup>	-CO-O-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	H	2
13	E-66	H	THP <sup>3</sup>	-CO-O-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	H	2
14	E-67	H	THP <sup>3</sup>	-CO-O-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	H	2
15	E-70	H	THP <sup>3</sup>	-CO-NH	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	Et	2
16	E-72	H	THP <sup>3</sup>	-CO-NH-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	Et	2
17	E-74	H	THP <sup>3</sup>	-CO-NH	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	H	2
18	E-75	H	THP <sup>3</sup>	-CO-NH	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	H	2
19	E-76	H	THP <sup>3</sup>	-CO-NH	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	H	2
20	E-77	H	THP <sup>3</sup>	-CO-NH	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	H	2
21	E-82	H	H	-CO-O-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	Benzyl	2

22

23 <sup>1</sup> 1,4-C<sub>6</sub>H<sub>4</sub> stands for 1,4-substituted phenyl24 <sup>2</sup> 2,6-C<sub>10</sub>H<sub>6</sub> stands for 2,6-substituted naphthalene25 <sup>3</sup> THP stands for 2-(1-tetrahydropyranyl).26 <sup>4</sup> polyene stands for -C(CH<sub>3</sub>)=CH-CH=CH-(CH<sub>3</sub>)=CH-

27

28 Referring now to compounds in accordance with Formula 2,

29 compounds in these series are preferred where the two X<sub>2</sub>R<sub>18</sub> jointly30 symbolize an oxo (=O) group, or where the two X<sub>2</sub>R<sub>18</sub> groups each31 symbolize an S-alkyl group, or where where the two X<sub>2</sub>R<sub>18</sub> groups jointly

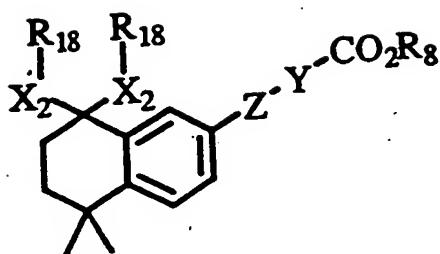
32 symbolize two sulphur atoms connected with a alkyledene bridge as in a

33 cyclic thioketal function.

34 The most preferred compounds in accordance with Formula 2 are

35 listed below in the Table for Formula 2A and with reference to that

36 formula.



Formula 2A

TABLE FOR FORMULA 2A

Compound	No.	X <sub>2</sub>	R <sub>18</sub>	Z	Y	R <sub>8</sub>
A-2		O <sup>1</sup>	--	-CH=CH-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>2</sup>	Et
A-2a		O <sup>1</sup>	--	-CH=CH-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>2</sup>	H
A-23		S	(CH <sub>2</sub> ) <sub>3</sub> <sup>3</sup> -	-CH=CH-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>2</sup>	Et
A-24		S	(CH <sub>2</sub> ) <sub>3</sub> <sup>3</sup> -	-CH=CH-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>2</sup>	H
B-1		--	H <sup>4</sup>	---	2,6-C <sub>10</sub> H <sub>6</sub> <sup>5</sup>	Et
B-2		--	H <sup>4</sup>	---	2,6-C <sub>10</sub> H <sub>6</sub> <sup>5</sup>	H
B-6		O <sup>1</sup>	--	---	2,6-C <sub>10</sub> H <sub>6</sub> <sup>5</sup>	Et
B-7		O <sup>1</sup>	--	---	2,6-C <sub>10</sub> H <sub>6</sub> <sup>5</sup>	H
C-5		O <sup>1</sup>	--	polyene <sup>6</sup>	--	Et
D-10		O <sup>1</sup>	--	-N=N-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>2</sup>	Et
E-28		O <sup>1</sup>	--	-CO-NH-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>2</sup>	Et
E-29		O <sup>1</sup>	--	-CO-NH-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>2</sup>	H
E-36		O <sup>1</sup>	--	-COO-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>2</sup>	(CH <sub>2</sub> ) <sub>2</sub> Si(CH <sub>3</sub> ) <sub>3</sub>
E-44		O <sup>1</sup>	--	-COO-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>2</sup>	Et
E-81		O <sup>1</sup>	--	-COO-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>2</sup>	benzyl



<sup>1</sup> The two  $X_2-R_{18}$  jointly symbolize an oxo ( $=O$ ) group;

<sup>2</sup>  $1,4-C_6H_4$  stands for 1,4-substituted phenyl;

<sup>3</sup> The three methylene groups form a propylene bridge;

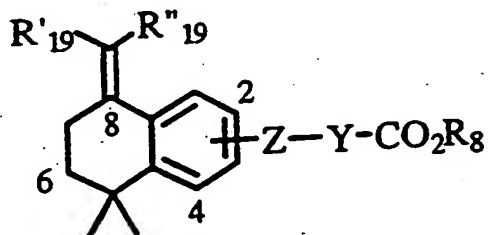
<sup>4</sup> Each of the two  $X_2R_{18}$  groups is H;

<sup>5</sup>  $2,6-C_{10}H_6$  stands for 2,6-substituted naphthalene.

<sup>6</sup> polyene stands for  $-C(CH_3)=CH-CH=CH-(CH_3)=CH-$

Compounds in accordance with Formula 3 are preferred where the  $R_9$  groups are alkyl, especially lower alkyl, most preferably methyl or ethyl, where the two  $R_{19}$  groups together with the methylenedene carbon form a 5 or 6 membered ring, and where the  $R_9$  groups are phenyl. Compounds are also preferred in accordance with this formula where one of the  $R_9$  groups is  $COOR_8$  or  $COOH$ , and the other is H.

The most preferred compounds in accordance with Formula 3 are listed below in the Table for Formula 3A and with reference to that formula.



Formula 3A

TABLE FOR FORMULA 3A

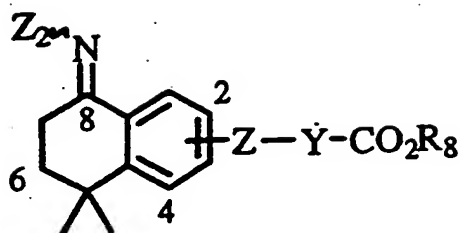
Compound No.	$R_{10}'$	$R_{10}$	Z	Y	$R_8$	Configuration when applicable and/or position of substituent
A-25	CH <sub>3</sub>	CH <sub>3</sub>	-CH=CH-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	Et	2
A-26	CH <sub>3</sub>	CH <sub>3</sub>	-CH=CH-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	H	2
A-27	CH <sub>2</sub> CH <sub>3</sub>	CH <sub>2</sub> CH <sub>3</sub>	-CH=CH-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	Et	2
A-28	CH <sub>2</sub> CH <sub>3</sub>	CH <sub>2</sub> CH <sub>3</sub>	-CH=CH-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	H	2
A-29	(CH <sub>2</sub> ) <sub>5</sub> <sup>2</sup>	--	-CH=CH-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	Et	2
A-31	(CH <sub>2</sub> ) <sub>5</sub> <sup>2</sup>	--	-CH=CH-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	H	2
C-17a	COOEt	H	polyene <sup>3</sup>	--	Et	2, <i>anti</i>
C-17b	COOEt	H	polyene <sup>3</sup>	--	Et	2, <i>syn</i>
C-36	CH <sub>3</sub>	CH <sub>3</sub>	polyene <sup>3</sup>	--	Et	2
C-41	phenyl	phenyl	polyene <sup>3</sup>	--	Et	2
D-2a	COOEt	H	-N=N-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	Et	2
D-23	CH <sub>3</sub>	CH <sub>3</sub>	-CO-CH=CH-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	H	3
E-13	CH <sub>3</sub>	CH <sub>3</sub>	-COO-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	CH <sub>2</sub> CH <sub>2</sub> SiMe <sub>3</sub>	2
E-14	CH <sub>3</sub>	CH <sub>3</sub>	-COO-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	H	2
E-15	CH <sub>3</sub>	CH <sub>3</sub>	-COO-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	Et	2
E-16	CH <sub>3</sub>	CH <sub>3</sub>	-CONH-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	Et	2
E-17	CH <sub>3</sub>	CH <sub>3</sub>	-CONH-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	H	2
E-50a	COOEt	H	-CONH-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	Et	2
E-52	COOH	H	-CONH-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	H	2, <i>cis</i>
E-53	COOH	H	-CONH-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	H	2, <i>trans</i>

<sup>1</sup> 1,4-C<sub>6</sub>H<sub>4</sub> stands for 1,4-substituted phenyl

<sup>2</sup> The 5-methylene groups together with the methylenedene group form a 6-membered ring.

<sup>3</sup> polyene stands for C(CH<sub>3</sub>)=CH-CH=CH-C(CH<sub>3</sub>)=CH-

Referring now to compounds in accordance with Formula 4, compounds in these series are preferred where the Z<sub>2</sub> group is O-lower alkyl, especially OCH<sub>3</sub> or OCH<sub>2</sub>CH<sub>3</sub>. The most preferred compounds in accordance with Formula 4 are listed below in the Table for Formula 4A and with reference to that formula.



Formula 4A

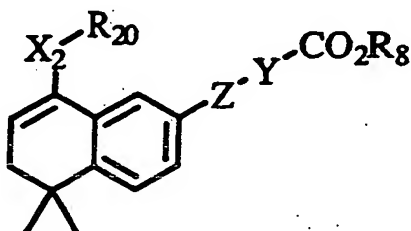
TABLE FOR FORMULA 4A

11						Position of Z
12						Substituent
13						and/or
14	Compound					configuration as
15	No.	Z <sub>2</sub>	Z	Y	R <sub>8</sub>	Applicable
16						
17	A-3	OCH <sub>3</sub>	-CH=CH-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	Et	2, <i>anti</i>
18	A-4	OCH <sub>3</sub>	-CH=CH-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	H	2, <i>anti</i>
19	A-5	OCH <sub>2</sub> CH <sub>3</sub>	-CH=CH-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	Et	2, <i>anti</i>
20	A-6	OCH <sub>3</sub> CH <sub>3</sub>	-CH=CH-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	H	2, <i>anti</i>
21	A-7	OH	-CH=CH-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	Et	2, <i>anti</i>
22	A-8	OH	-CH=CH-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	H	2, <i>anti</i>
23	B-11	OCH <sub>3</sub>	--	2,6-C <sub>10</sub> H <sub>6</sub> <sup>2</sup>	Et	2, <i>anti</i>
24	B-12	OCH <sub>3</sub>	--	2,6-C <sub>10</sub> H <sub>6</sub> <sup>2</sup>	H	2, <i>anti</i>
25	C-6	OCH <sub>3</sub>	polyene <sup>3</sup>	--	Et	2, <i>anti</i>
26	C-22a	OCH <sub>3</sub> CH <sub>3</sub>	polyene <sup>3</sup>	--	Et	2, <i>syn</i>
27	C-22b	OCH <sub>2</sub> CH <sub>3</sub>	polyene <sup>3</sup>	--	Et	2, <i>anti</i>
28	C-24	OCH <sub>2</sub> CH <sub>3</sub>	polyene <sup>3</sup>	--	H	2, <i>syn</i>
29	C-25	OCH <sub>2</sub> CH <sub>3</sub>	polyene <sup>3</sup>	--	H	2, <i>anti</i>
30	D-3	OCH <sub>3</sub>	-N=N-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	Et	2, <i>anti</i>
31	D-4	OCH <sub>3</sub>	-N=N-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	H	2, <i>anti</i>
32	D-29	OCH <sub>3</sub>	-CO-CH=CH-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	H	3
33	E-30	OCH <sub>3</sub>	-CONH-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	Et	2, <i>anti</i>
34	E-31	OCH <sub>3</sub>	-CONH-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	H	2, <i>anti</i>
35	E-42	OCH <sub>3</sub>	-COO-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> (CH <sub>3</sub> ) <sub>3</sub> SiMe <sub>3</sub>		2, <i>anti</i>
36	E-43	OCH <sub>3</sub>	-COO-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	H	2, <i>anti</i>
37	E-46	OCH <sub>3</sub>	-COO-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	Et	2, <i>anti</i>
38						

- 1 <sup>1</sup> stands for 1,4-substituted phenyl  
 2 <sup>2</sup> stands for 2,6-substituted naphthyl  
 3 <sup>3</sup> polyene stands for  $C(CH_3)=CH-CH=CH-C(CH_3)=CH-$   
 4

5 Compounds in accordance with Formula 5 are preferred where  
 6 the  $R_{20}$  group is lower alkyl, phenyl or  $SO_2CF_3$ .

7 The most preferred compounds in accordance with Formula 5 are  
 8 listed below in the Table for Formula 5A and with reference to that  
 9 formula.



15 Formula 5A

16 TABLE FOR FORMULA 5A

17	Compound					
18	No.	$X_2$	$R_{20}$	Z	Y	$R_8$
19	A-9	O	$SO_2CF_3$	$-CH=CH-$	$1,4-C_6H_4^1$	Et
20	A-16	S	phenyl	$-CH=CH-$	$1,4-C_6H_4^1$	Et
21	A-18	S	phenyl	$-CH=CH-$	$1,4-C_6H_4^1$	H
22	A-17	$SO_2$	phenyl	$-CH=CH-$	$1,4-C_6H_4^1$	Et
23	A-19	$SO_2$	phenyl	$-CH=CH-$	$1,4-C_6H_4^1$	H
24	A-20	S	$CH_2CH_3$	$-CH=CH-$	$1,4-C_6H_4^1$	Et
25	A-21	S	$CH_2CH_3$	$-CH=CH-$	$1,4-C_6H_4^1$	H
26	A-22	$SO_2$	$CH_2CH_3$	$-CH=CH-$	$1,4-C_6H_4^1$	H
27	C-10	S	phenyl	polyene <sup>2</sup>	--	Et
28	C-11	$SO_2$	phenyl	polyene <sup>2</sup>	--	Et
29	C-12	SO	phenyl	polyene <sup>2</sup>	--	Et

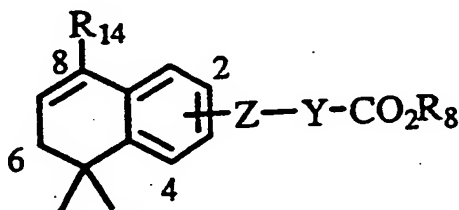
1	C-14	O	SO <sub>2</sub> CF <sub>3</sub>	polyene <sup>2</sup>	--	Et
2	C-28	O	trimethylsilyl	polyene <sup>2</sup>	--	Et
3	D-11	O	SO <sub>2</sub> CF <sub>3</sub>	-N=N-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	Et
4	E-20	S	phenyl	-CONH-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	Et
5	E-21	S	phenyl	-CONH-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	H
6	E-22	SO <sub>2</sub>	phenyl	-CONH-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	H
7	E-23	S	phenyl	-COO-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	Et
8	E-24	SO <sub>2</sub>	phenyl	-COO-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	Et
9	E-25	S	phenyl	-COO-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	(CH <sub>2</sub> ) <sub>2</sub> Si(CH <sub>3</sub> ) <sub>3</sub>
10	E-26	S	phenyl	-COO-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	H
11	E-27	SO <sub>2</sub>	phenyl	-COO-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	H

12 <sup>1</sup> stands for 1,4-substituted phenyl

13 <sup>2</sup> polyene stands for C(CH<sub>3</sub>)=CH-CH=CH-(CH<sub>3</sub>)=CH

14 Referring now to compounds in accordance with Formula 6,  
 15 compounds in these series are preferred where the R<sub>14</sub> group is  
 16 thiazolyl, more preferably 2-thiazolyl, thienyl, more preferably 2-thienyl,  
 17 branched chain lower alkyl, more preferably *t*-butyl, or where R<sub>14</sub> is  
 18 CH<sub>2</sub>COOR<sub>8</sub> or CH<sub>2</sub>COOH.

19 The most preferred compounds in accordance with Formula 6 are  
 20 listed below in the Table for Formula 6A and with reference to that  
 21 formula.



28 Formula 6A

TABLE FOR FORMULA 6A

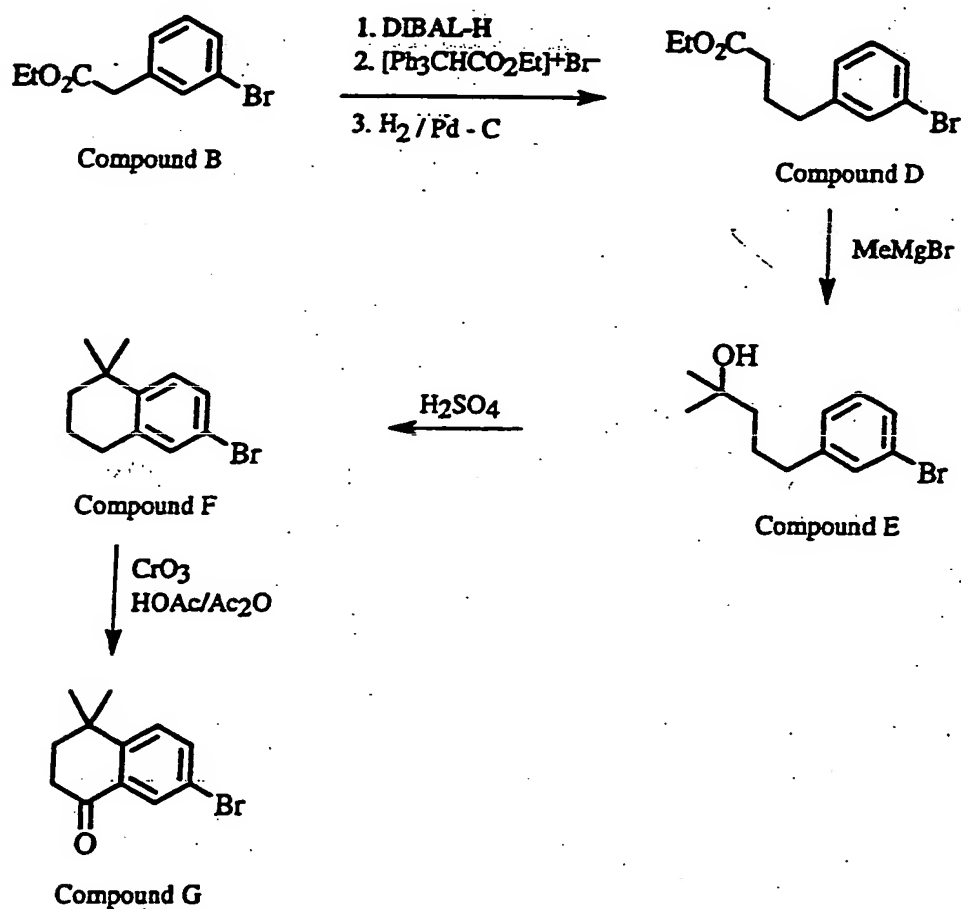
Compound No.	R <sub>14</sub>	Z	Y	R <sub>8</sub>	Position of Z Substituent
A-10	2-thiazolyl	-CH=CH-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	Et	2
A-12	2-thiazolyl	-CH=CH-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	H	2
A-13	2-thienyl	-CH=CH-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	Et	2
A-15	2-thienyl	-CH=CH-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	H	2
C-15	2-thienyl	polyene <sup>2</sup>	--	Et	2
C-20	2-thienyl	polyene <sup>2</sup>	--	H	2
C-46	t-butyl	polyene <sup>2</sup>	--	Et	2
D-2b	CH <sub>2</sub> COOEt	-N=N-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	Et	2
D-12	2-thienyl	-N=N-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	Et	2
D-13	2-thienyl	-N=N-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	H	2
D-18	CH <sub>2</sub> COOEt	CO-CH=CH-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	H	3
D-20	t-butyl	-CO-CH=CH-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	H	3
D-34	2-thienyl	CO-CH=CH-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	H	3
E-7	2-thienyl	-CO-NH-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	Et	2
E-8	2-thienyl	-CO-NH-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	H	2
E-9	2-thienyl	-COO-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	Et	2
E-10	2-thienyl	-COO-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	(CH <sub>2</sub> ) <sub>2</sub> SiMe <sub>3</sub>	2
E-11	2-thienyl	-COO-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	H	2
E-50b	CH <sub>2</sub> -COOEt	-CO-NH-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	Et	2
E-55	CH <sub>2</sub> COOEt	-COO-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	Et	2
E-79	t-butyl	-CO-NH-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	Et	2
E-80	t-butyl	-CO-NH-	1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>	H	2

<sup>1</sup> stands for 1,4-substituted phenyl

<sup>2</sup> polyene stands for C(CH<sub>3</sub>)=CH-CH=CH-C(CH<sub>3</sub>)=CH-

The compounds of this invention can be made by the general procedures outlined above under the title "GENERAL EMBODIMENTS AND SYNTHETIC METHODOLOGY". The following chemical pathways represent the presently contemplated best synthetic routes to certain exemplary compounds of the invention

illustrated here. However, the synthetic chemist will readily appreciate that the conditions set out here for these specific embodiments can be generalized to any and all of the compounds represented by Formulas 1 through 6.



Reaction Scheme 1

1           Important starting materials for the synthesis of the preferred  
2   compounds of the invention are  
3   6-bromo-1,2,3,4-tetrahydro-1,1-dimethylnaphthalene (Compound F),  
4   7-bromo-3,4-dihydro-4,4-dimethylnaphthalen-1-one (Compound G), and  
5   the isomeric bromo compound,  
6   6-bromo-3,4-dihydro-4,4-dimethylnaphthalen-1(2H)-one (Compound H).  
7   Compound G can be obtained as described in *J. Med. Chem.* 1995, 38,  
8   4764 - 4767, and as shown in Reaction Scheme 1. Thus, referring now  
9   specifically to Reaction Scheme 1, ethyl 3-bromophenylacetate  
10   (Compound B, made by esterification of 3-bromophenylacetic acid) is  
11   reduced with diisobutylaluminum hydride (DIBAL H) to yield  
12   (3-bromophenyl)acetaldehyde. (3-Bromophenyl)acetaldehyde is reacted  
13   in a *Wittig* reaction with (carbethoxymethylene)triphenylphosphorane to  
14   provide a mixture of E and Z ethyl 4-(3-bromophenyl)but-2-enoates.  
15   The latter compounds are hydrogenated to yield ethyl  
16   4-(3-bromophenyl)butanoate (Compound D). Compound D is reacted  
17   with the Grignard reagent derived from methylbromide to give the  
18   tertiary alcohol 5-(3-bromophenyl)-2-methylpentan-2-ol (Compound E)  
19   (It should be apparent to those skilled in the art, that the choice of the  
20   Grignard reagent used in this reaction step determines the nature of the  
21   R<sub>1</sub> substituent in the resulting compounds of the invention.) Compound  
22   E is then treated with acid to cyclize it and to form  
23   6-bromo-1,2,3,4-tetrahydro-1,1-dimethylnaphthalene (Compound F).  
24   Compound F is oxidized with chromium trioxide to yield  
25   7-bromo-3,4-dihydro-4,4-dimethylnaphthalen-1(2H)-one (Compound G).  
26   The isomeric compound,  
27   6-bromo-3,4-dihydro-4,4-dimethylnaphthalen-1(2H)-one (Compound H)  
28   can be obtained, starting with ethyl (4-bromophenyl)acetate, in



1 accordance with the sequence of reactions illustrated in Reaction  
2 Scheme 1 for Compound G.  
3 6-Bromo-3,4-dihydro-4,4-dimethylnaphthalen-1(2H)-one (Compound H)  
4 can also be obtained in accordance with the published literature  
5 procedure: Mathur et al. Tetrahedron, 41, 1509-1516 (1985).

6 Another important starting material for the synthesis of several  
7 preferred compounds of the invention is 3,4-dihydro-4,4-dimethyl-7-  
8 aminonaphthalen-1(2H)-one (Compound D9) which is prepared from  
9 the known 3,4-dihydro-4,4-dimethylnaphthalen-1(2H)-one, by nitration  
10 and subsequent catalytic reduction of the intermediate 3,4-dihydro-4,4-  
11 dimethyl-7-nitronaphthalen-1(2H)-one (Compound D8), as is described  
12 in the enclosed description of specific examples.

13 Still other important starting materials for the synthesis of several  
14 preferred compounds of the invention are the isomeric 3,4-dihydro-4,4-  
15 dimethyl-7-acetyl-naphthalen-1(2H)-one (Compound D14a); and 3,4-  
16 dihydro-4,4-dimethyl-6-acetyl-naphthalen-1(2H)-one (Compound D14b).  
17 These are prepared by reacting 1,2,3,4-tetrahydro-1,1-  
18 dimethylnaphthalene with acetyl chloride in a Friedel-Crafts type  
19 reaction, followed by oxidation with chromium trioxide of the isomeric  
20 acetyl derivatives. These compounds can also be obtained by an  
21 alternative procedure from Compounds G and H respectively. The  
22 experimental conditions of these preparations are disclosed in the  
23 description of the specific examples.

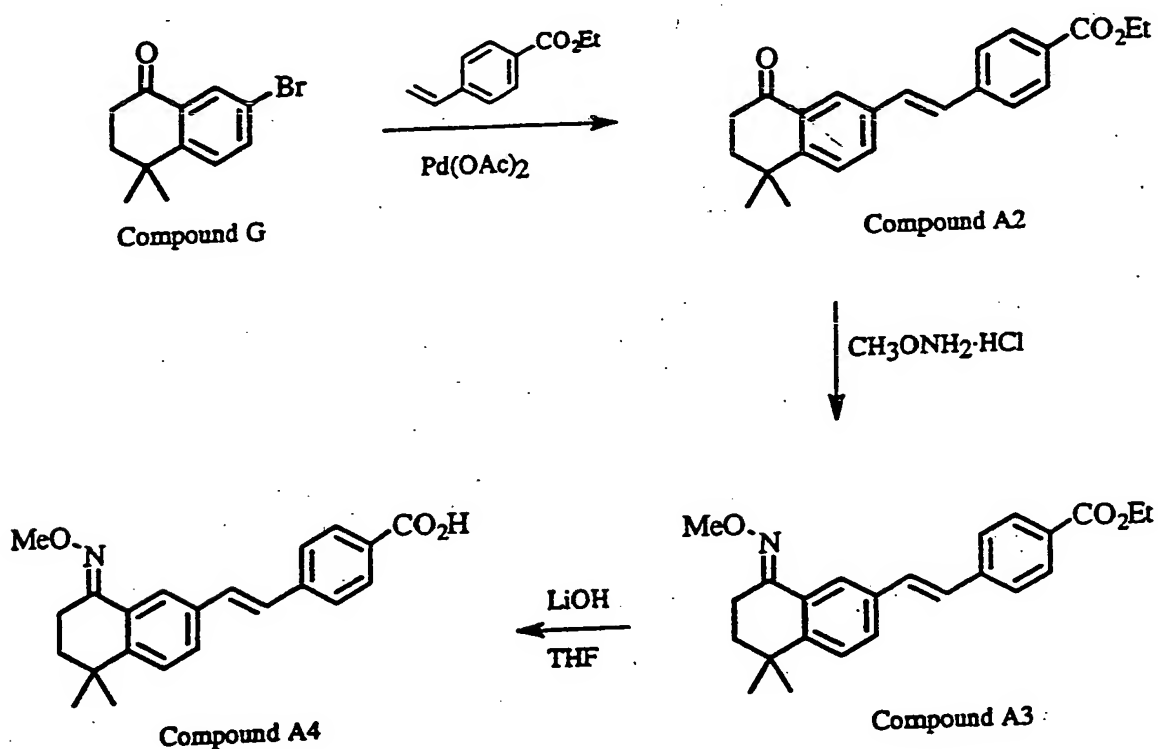
24 Yet another important starting material for the synthesis of  
25 several preferred compounds of the invention is methyl 5,5-dimethyl-5,6-  
26 dihydro-naphthalen-8(7H)-one-2-carboxylate (Compound E2) which can  
27 be made by reaction of  
28 7-bromo-3,4-dihydro-4,4-dimethylnaphthalen-1-one (Compound G) with

1 CO<sub>2</sub> in the presence of *t*-butyl lithium, but is more advantageously  
2 prepared in the presence of palladium(II)-  
3 bis(triphenylphosphine)chloride and 1,3-bis(diphenylphosphino)propane  
4 catalysts by reaction with carbonmonoxide and methanol, as is described  
5 in the specific examples.

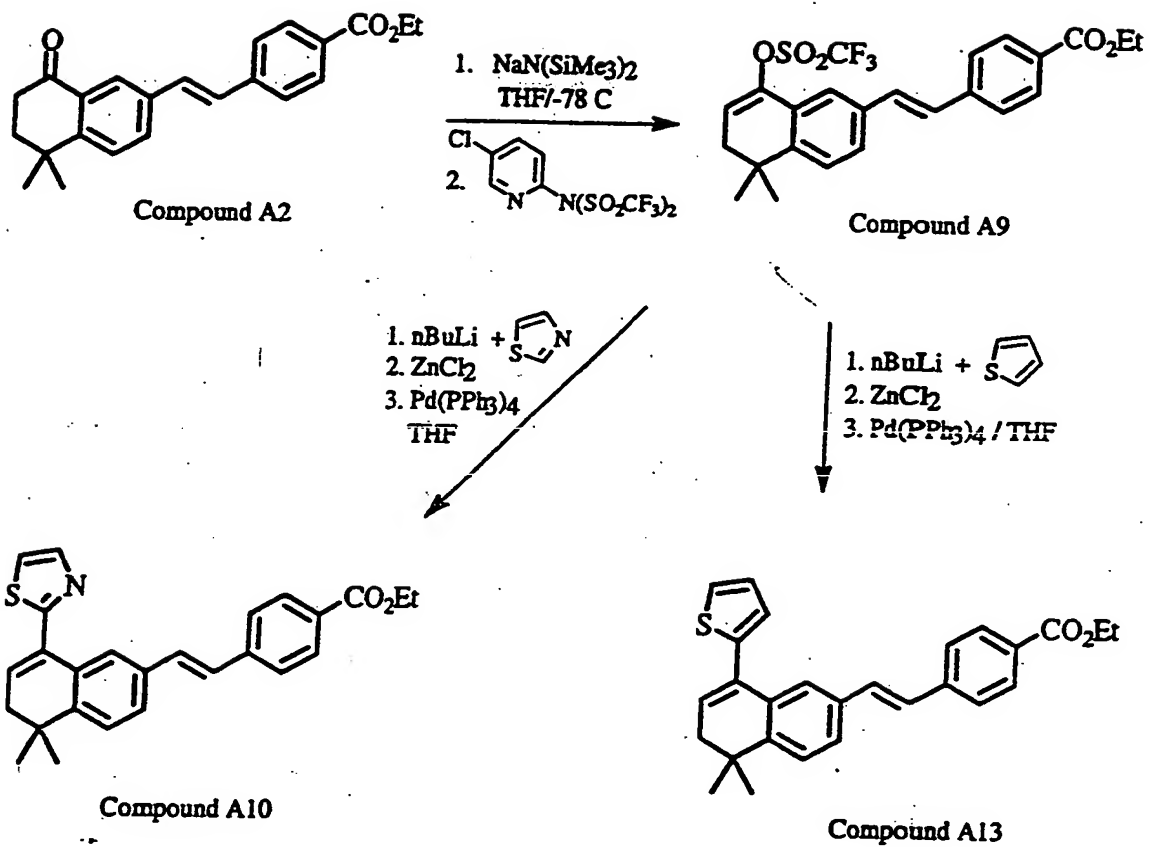
6 Referring now to Reaction Scheme 2 the synthesis of preferred  
7 examples of compounds of the invention are described, where the Z  
8 group, with reference to Formulas 1 - 6 is -CH=CH-. Compounds of  
9 this type of the invention are advantageously obtained in a direct  
10 coupling reaction between an ethenyl compound such as ethyl 4-  
11 vinylbenzoate, and a 6- or 7-bromonaphthalene-1(2H)-one derivative,  
12 such as Compound G or Compound H in a reaction commonly known  
13 as the *Heck* reaction. Reaction Scheme 2 exemplifies this reaction with  
14 7-bromo-3,4-dihydro-4,4-dimethylnaphthalen-1(2H)-one (Compound G)  
15 as the starting material. A general formula for the ethenyl compounds  
16 which are suitable as reagents in the *Heck* reaction to provide these type  
17 of compounds of the invention is CH<sub>2</sub>=CH<sub>2</sub>-Y(R<sub>2</sub>)-A-B where the  
18 symbols have the same meaning as defined in connection with Formulas  
19 1 - 6. These compounds are readily available in accordance with the  
20 chemical literature, or otherwise in accordance with state-of-the-art.  
21 The *Heck* reaction is well known in the art, and is usually conducted in  
22 a basic solvent, such as triethylamine, in the presence of a phosphine  
23 catalyst (such as tris(2-methylphenyl)phosphine or tri-*O*-tolylphosphine)  
24 in the presence of palladium(II)acetate catalyst.

25 Those skilled in the art will readily understand that the  
26 compounds of the invention which have an ethylene (-CH=CH-) or  
27 substituted ethylene (-CR<sub>1</sub>=CR<sub>1</sub>-) linking group can also be made by a  
28 Wittig or like (*Horner Emmons*) reactions, which are *per se* well known

1 in the art. Those skilled in the art will also readily understand that the  
2 reaction sequence shown in Reaction Scheme 2 can be readily adapted  
3 for compounds where the tetrahydronaphthalene (or other rings within  
4 the scopes of Formulas 1 - 6) have  $R_1$ ,  $R_2$  and  $R_3$  substituents other than  
5 specifically shown in this reaction scheme.



Reaction Scheme 2



Reaction Scheme 2 (continued)

1           Thus in the example shown in Reaction Scheme 2

2    7-bromo-3,4-dihydro-4,4-dimethylnaphthalen-1(2H)-one (Compound G)  
3    is reacted with ethyl 4-vinylbenzoate to yield ethyl (E)-4-[2-(5,6-dihydro-  
4    5,5-dimethylnaphthalen-8(7H)-one-2-yl)ethenyl]-benzoate (Compound  
5    A2). Ethyl 4-vinylbenzoate is available in accordance with the chemical  
6    literature, Can. J. Chem (1973) 51, 897 - 914, which is expressly  
7    incorporated herein by reference. Compound A2 is an example for the  
8    compounds of the present invention within the scope of Formula 2.

9    Compound A2 is reacted with methoxylamine hydrochloride in an  
10   alcoholic solvent (such as ethanol) in the presence of sodium acetate to  
11   yield the methyl oxime, ethyl (E)-4-[2-(5,5-dimethyl-5,6,-dihydro-8(7H)-  
12   *anti*-(O-methyl oxime)-naphthalen-2-yl)ethenyl]-benzoate (Compound  
13   A3). Compound A3 can be saponified by treatment with base, such as  
14   LiOH, to provide the free carboxylic acid, (E)-4-[2-(5,5-dimethyl-5,6,-  
15   dihydro-8(7H)-*anti*-(O-methyl oxime)-naphthalen-2-yl)ethenyl]-benzoic  
16   acid (Compound A4). Compounds A3 and A4 are compounds of the  
17   invention within the scope of Formula 4. The conditions for the  
18   saponification of Compound A3 to provide Compounds A4 serve as  
19   example for several saponification reactions which yield several  
20   compounds of the invention where the B group of Formulas 1 - 6 is a  
21   free carboxylic acid (COOH), or salt thereof.

22       Instead of methoxylamine hydrochloride, hydroxylamine  
23   hydrochloride, or ethoxylamine hydrochloride or other analogous  
24   reagents can be used to obtain the oximes or other O-alkyl, O-aryl  
25   analogs of Compounds A3 and A4, within the scope of Formula 4.  
26   Generally speaking and with reference to Formula 4, the oxo  
27   compounds, such as Compound A2 are reacted with a reagent of the  
28   formula  $\text{NH}_2\text{-Z}_2$ , where  $\text{Z}_2$  is defined as in connection with Formula 4.

1 Thus, the oxo compounds analogous to **Compound A2** are reacted with  
 2 a reagent of the formula  $H_2N-Z_2$  to yield compounds of **Formula 4**. As  
 3 is known, when the reagent  $H_2N-Z_2$  is  $NH_2OH$  or its salt, then the  
 4 reaction is the formation of an oxime. Generally speaking the oximes  
 5 are readily formed by reacting the oxo compounds with hydroxylamine  
 6 hydrochloride in a polar solvent, such as a lower alkanol, in the  
 7 presence of a buffering agent, such as sodium acetate. The reaction can  
 8 be conducted under similar conditions with a reagent of the formula  
 9  $NH_2OR_1$  or its salt (such as methoxylamine hydrochloride or  
 10 ethoxylamine hydrochloride as demonstrated in **Reaction Scheme 2**) to  
 11 yield compounds of **Formula 4** where  $Z_1$  is  $OR_1$  ( $R_1$  is defined as in  
 12 connection with **Formula 4**). When the reagent  $H_2N-Z_2$  is a primary  
 13 amine then the reaction is the formation of an imine. The latter  
 14 reaction is usually conducted in a polar (alcoholic) solvent. Further  
 15 reagents, in accordance with the general formula  $H_2NZ_2$ , are those  
 16 where  $Z_2$  is  $NHCON(R_{14})_2$  (formation of semicarbazone),  $NHCSN(R_{14})_2$   
 17 (formation of thiosemicarbazone) and  $N(R_{14})_2$  (formation of a  
 18 hydrazone). (The symbol  $R_{14}$  is defined as in connection with **Formula**  
 19 **4**.) The semicarbazones, thiosemicarbazones and hydrazones  
 20 corresponding to **Formula 4** can be prepared under conditions which  
 21 are well known in the art for the formation of such derivatives of  
 22 ketone compounds. Usually these conditions are similar to the  
 23 conditions leading to the oximes described above. Typically, the  
 24 hydrochloride salt of the reagent (semicarbazide, thiosemicarbazide or  
 25 hydrazide) is reacted with the oxo compound such as **Compound A2** in  
 26 an alcoholic solvent, in the presence of sodium acetate.

27 Referring now again specifically to **Reaction Scheme 2**, ethyl (E)-  
 28 4-[2-(5,6-dihydro-5,5-dimethylnaphthalen-8(7H)-one-2-yl)ethenyl]-

1 benzoate (Compound A2) is reacted with sodium  
 2 bis(trimethylsilyl)amide and 2-[N,N-bis(trifluoromethane-  
 3 sulfonyl)amino]-5-chloropyridine in an inert ether type solvent, such as  
 4 tetrahydrofuran, at low temperatures (-78°C and 0°C). This provides  
 5 first a sodium salt intermediate which is not isolated and not shown in  
 6 the reaction scheme. The reactions ultimately result in the  
 7 trifluoromethylsulfonyloxy derivative ethyl (E)-4-[2-(5,6-dihydro-5,5-  
 8 dimethyl-8-(trifluoromethylsulfonyl)oxy-naphthalen-2-yl)ethenyl]-  
 9 benzoate (Compound A9). Compound A9 is within the scope of  
 10 Formula 5 of the present invention and is also an important  
 11 intermediate for the synthesis of several compounds of the invention  
 12 within the scope of Formula 6. Compound A9 is a  
 13 trifluoromethylsulfonate derivative, which sometimes also called a  
 14 "triflate" in the trade, and the  $\text{CF}_3\text{SO}_2$  group is sometimes abbreviated  
 15 as "Tf" in the reaction schemes.

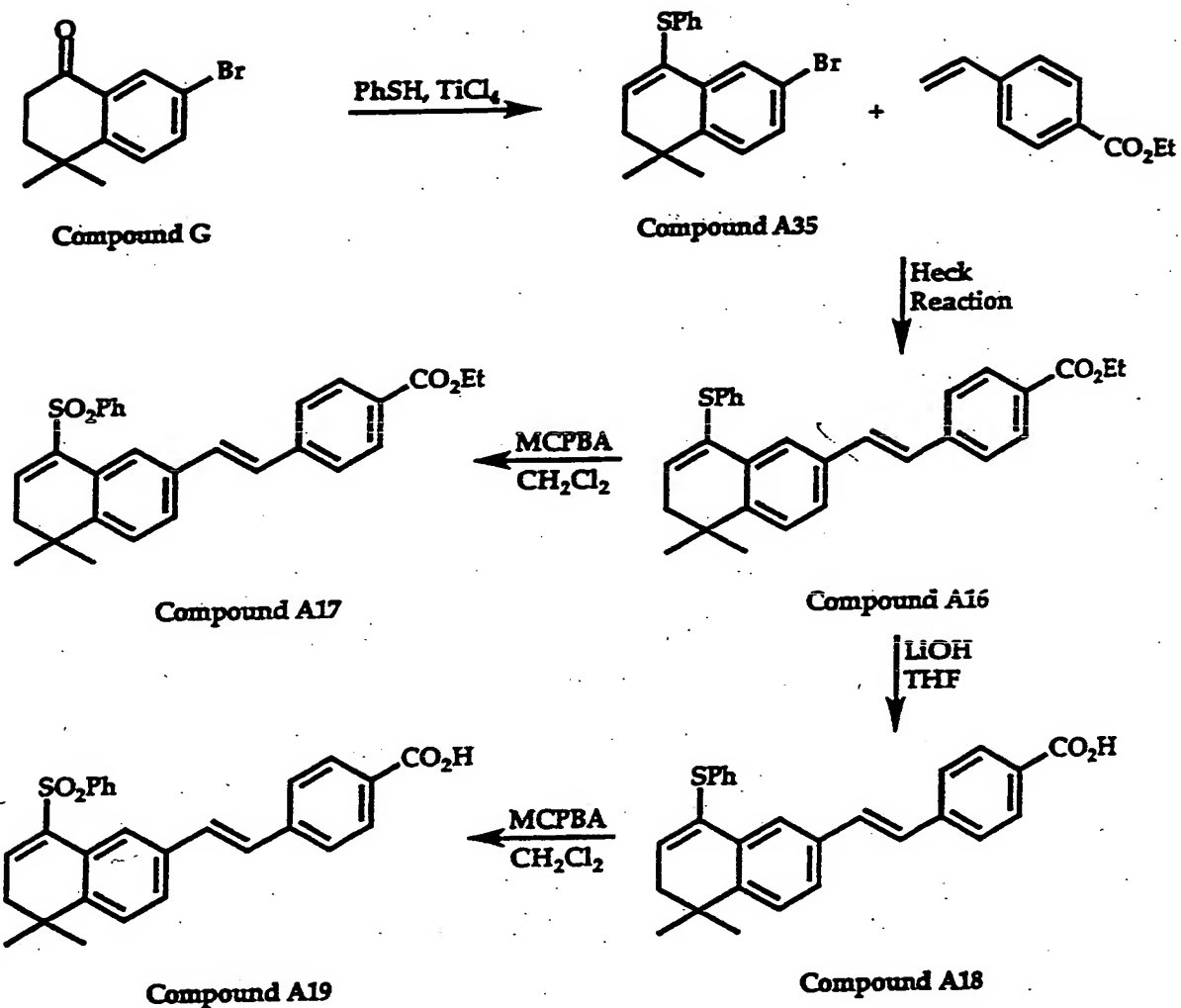
16 As is shown further in Reaction Scheme 2 for the specific  
 17 examples of thiazole and thiophene, respectively yielding Compounds  
 18 A10 and A13, the triflate derivative Compound A9 is reacted with an  
 19 organometal derivative derived from the compound  $\text{R}_{14}\text{H}$ , such that the  
 20 formula of the organometal derivative is  $\text{R}_{14}\text{Met}$  (Met stands for  
 21 monovalent metal), preferably  $\text{R}_{14}\text{Li}$ . ( $\text{R}_{14}$  is defined as in connection  
 22 with Formula 6.) The reaction with the organometal derivative,  
 23 preferably lithium derivative of the formula  $\text{R}_{14}\text{Li}$  is usually conducted in  
 24 an inert ether type solvent (such as tetrahydrofuran) in the presence of  
 25 zinc chloride ( $\text{ZnCl}_2$ ) and tetrakis(triphenylphosphine)palladium(0)  
 26 ( $\text{Pd}(\text{PPh}_3)_4$ ). The organolithium reagent  $\text{R}_{14}\text{Li}$ , if not commercially  
 27 available, can be prepared from the compound  $\text{R}_{14}\text{H}$  (or its halogen  
 28 derivative  $\text{R}_{14}\text{-X}_1$  where  $\text{X}_1$  is halogen) in an ether type solvent in

1 accordance with known practice in the art. The temperature range for  
2 the reaction between the reagent  $R_4Li$  and the triflate derivatives is,  
3 generally speaking in the range of approximately  $-78^{\circ}C$  to  $50^{\circ}C$ .

4 Compounds A10 and A13 and their analogs can be saponified, or  
5 subjected to further transformations, such as homologation and other  
6 state-of-the-art reactions which yield homologs and derivatives in  
7 accordance with the reactions discussed above.

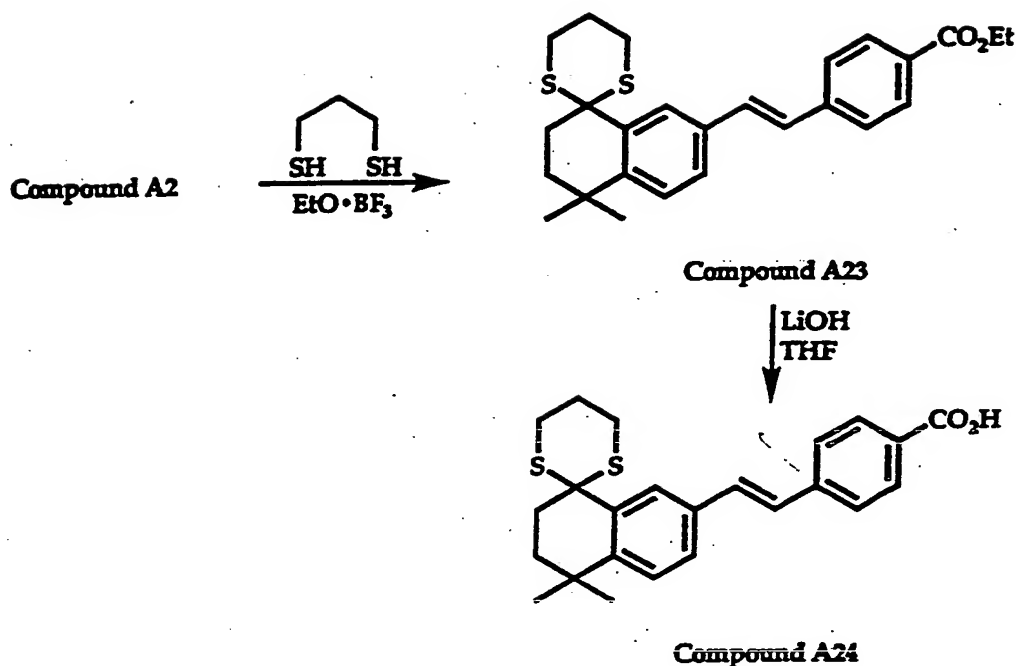
8       **Reaction Scheme 2** serves as an example of synthetic  
9 methodology used for preparing compounds of the present invention  
10 where the  $-Y(R_2)-A-B$  group of Formulas 1 - 6 is linked to the  
11 tetrahydronaphthalene nucleus with the desired Z group, before the  
12 final substitution pattern is obtained by transformations of the  
13 tetrahydronaphthalene (or dihydronaphthalene) moiety.





Reaction Scheme 3

1           **Reaction Scheme 3** provides further examples for the synthesis of  
2 compounds within the scope of **Formula 5** where the linking group  
3 between the dihydronaphthalene moiety and the Y group is  $-\text{CH}=\text{CH}-$ .  
4 In the sequence of reactions described here the oxo function of a  
5 starting tetrahydronaphthalene-one moiety is modified before a *Heck*  
6 coupling reaction is performed. Specifically, in the example shown in  
7 the reaction scheme,  
8 7-bromo-3,4-dihydro-4,4-dimethylnaphthalen-1(2H)-one (**Compound G**)  
9 is reacted with thiophenol in the presence of titanium tetrachloride and  
10 triethylamine in tetrahydrofuran (THF), to provide the intermediate 4,4-  
11 dimethyl-7-bromo-1-phenylthio-3,4-dihydronaphthalene (**Compound**  
12 **A35**). A similar reaction can be performed with ethanethiol as a  
13 reagent instead of thiophenol, to yield 2-bromo-5,6-dihydro-5,5-  
14 dimethyl-8-ethylthio-naphthalene (**Compound A36**) and other analogous  
15 compounds which are not shown in the reaction scheme. **Compound**  
16 **A35** is reacted in the *Heck* reaction to yield ethyl (E)-4-[2-(5,6-dihydro-  
17 5,5-dimethyl-8-phenylthio-naphthalenyl)ethenyl] benzoate (**Compound**  
18 **A16**). **Compound A16** is saponified to yield the carboxylic acid, (E)-4-  
19 [2-(5,6-dihydro-5,5-dimethyl-8-(phenylthio)-naphthalen-2-yl)ethenyl]  
20 benzoic acid (**Compound A18**), and is oxidized with *m*-  
21 chloroperoxybenzoic acid (MCPBA) to provide the corresponding  
22 phenylsulfonyl compound, ethyl (E)-4-[2-(5,6-dihydro-5,5-dimethyl-8-  
23 (phenylsulfonyl)-naphthalenyl)ethenyl]benzoate (**Compound A17**).  
24 **Compound A18** can also be oxidized under similar conditions to provide  
25 the free carboxylic acid (or salt thereof) of the phenylsulfonyl  
26 compound, (E)-4-[2-(5,6-dihydro-5,5-dimethyl-8-phenylsulfonyl-  
27 naphthalenyl)ethenyl]benzoic acid (**Compound A19**).



#### Reaction Scheme 4

Reaction Scheme 4 discloses further examples for the preparation of compounds of the invention within the scope of Formula 2 where the group linking the tetrahydronaphthalene and Y(R<sub>2</sub>)-A-B moieties is -CH=CH-. As is shown in the scheme, ethyl (E)-4-[2-(5,6-dihydro-5,5-dimethylnaphthalen-8(7H)-one-2-yl)ethenyl]benzoate (Compound A2) is reacted with 1,3-propanedithiol in the presence of borontrifluoride diethyl etherate to yield the corresponding cyclic thioketal compound, ethyl (E)-4-[-2-(5,6,7,8-tetrahydro-5,5-dimethyl-8-(1,3-dithian-2-

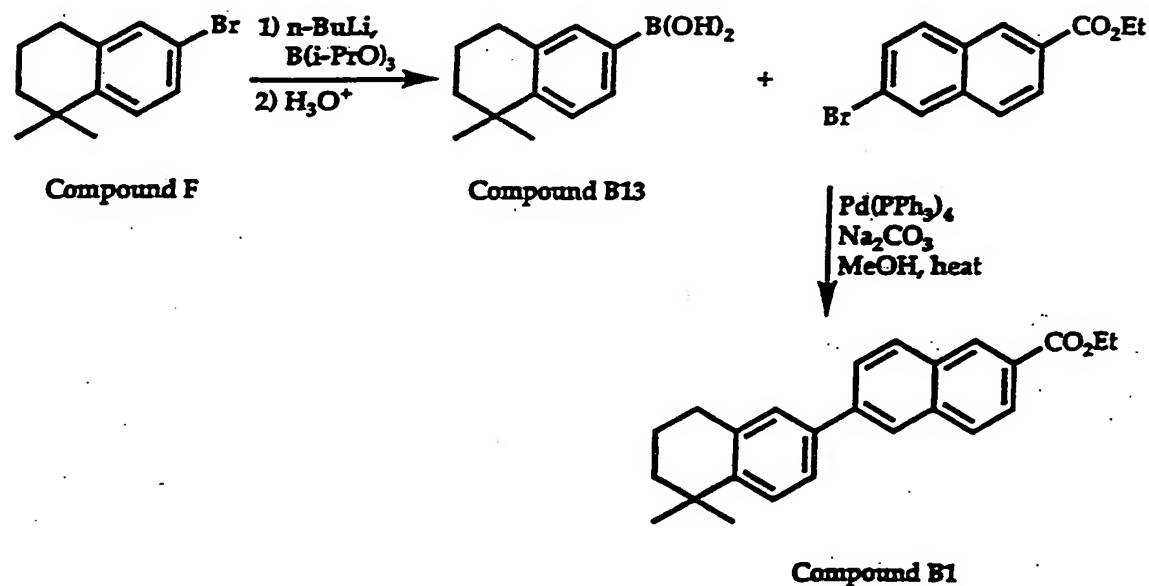
1 yl)naphthalen-2-yl)ethenyl] benzoate (Compound A23). Other ketal  
2 and thioketal analogs of this compound, within the scope of Formula 2  
3 can be obtained by analogous reactions suitable for ketal and thioketal  
4 formation, which are *per se* well known in the art. Saponification of  
5 Compound A23 provides the corresponding free acid (or salt thereof),  
6 (E)-4-[2-(5,6,7,8-tetrahydro-5,5-dimethyl-8-(2-(1,3-dithian-2-  
7 yl)naphthalenyl)ethenyl]-benzoic acid (Compound A24).



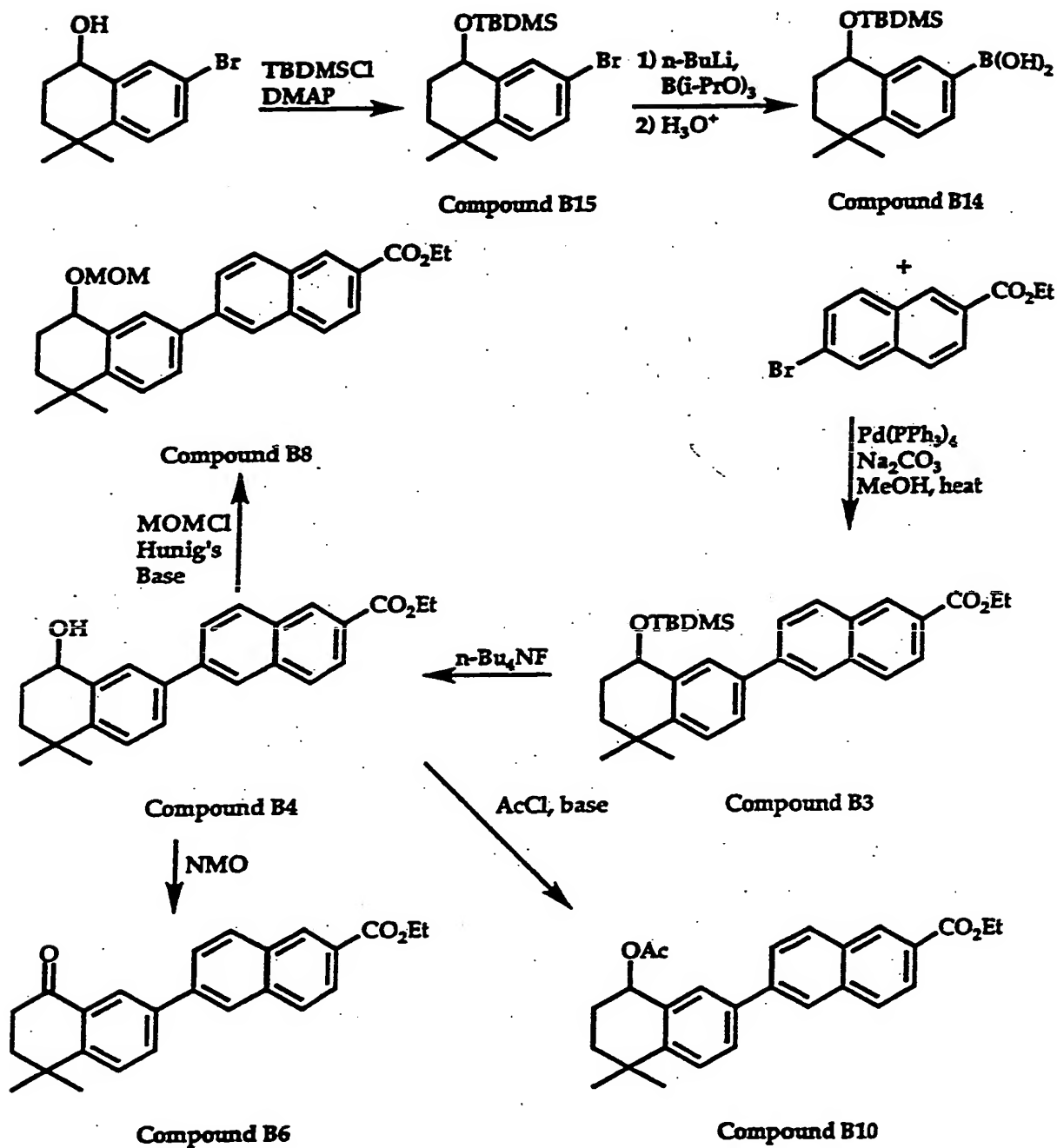
1           **Reaction Scheme 5** provides examples for the synthesis of  
2   compounds of the invention within the scope of **Formula 3**. The  
3   synthesis of these compounds proceeds in accordance with methodology  
4   where the desired substituent is introduced into the  
5   tetrahydronaphthalene moiety before this moiety is coupled or linked  
6   to the desired **Z-Y(R<sub>2</sub>)-A-B** group, and in these examples also the **Z**  
7   group is **-CH=CH-**. Thus in accordance with this scheme,  
8   **7-bromo-3,4-dihydro-4,4-dimethylnaphthalen-1(2H)-one (Compound G)**  
9   is reacted in a *McMurry* coupling reaction with acetone to provide 7-  
10   bromo-1(2H)-(propyliden-2-yl)-3,4-dihydro-4,4-dimethylnaphthalene  
11   (**Compound A37**). The reaction (*McMurry* coupling) is conducted at  
12   elevated temperature in the presence of lithium metal and titanium  
13   trichloride, in an inert ether type solvent, for example in refluxing  
14   1,2-dimethoxyethane (DME). In other examples which are described in  
15   the **Specific Examples**, 3-pentanone, and cyclohexanone are used as  
16   ketone reagents, instead of the acetone shown in the reaction scheme.  
17   **Compound A37** is then subjected to a *Heck* coupling reaction with an  
18   ethenyl reagent such as ethyl 4-vinylbenzoate shown in the scheme, to  
19   provide ethyl (E)-4-[2-(5,6-dihydro-5,5-dimethyl-8(7H)-(propyliden-2-yl)-  
20   naphthalen-2-yl)ethenyl]benzoate (**Compound A25**). **Compound A25** is  
21   saponified under conditions described above to provide (E)-4-[2-(5,6-  
22   dihydro-5,5-dimethyl-8(7H)-(propyliden-2-yl)-naphthalen-2-yl)ethenyl]-  
23   benzoic acid (**Compound A26**).

24           **Reaction Scheme 5** discloses another example for the preparation  
25   of compounds within the scope of **Formula 3**. In this example the  
26   substituent is introduced to replace the oxo function of  
27   tetrahydronaphthalene-2-one after the **Z-Y(R<sub>2</sub>)-A-B** group has already  
28   been coupled to the tetrahydronaphthalene nucleus. Thus, ethyl (E)-4-

1 [2-(5,6-dihydro-5,5-dimethyl-naphthalen-8(7H)-one-2-yl)ethenyl]-  
 2 benzoate (**Compound A2**) is reacted with ethyl bromoacetate in the  
 3 presence of zinc metal in a *Reformatsky* reaction to provide (+/-) ethyl  
 4 (E)-4-[2-(5,6,7,8-tetrahydro-5,5-dimethyl-8-hydroxy-8-  
 5 (carbethoxymethyl)naphthalen-2-yl)ethenyl] benzoate (**Compound A32**).  
 6 **Compound A32** is itself within the scope of the present invention, within  
 7 the scope of **Formula 1**. **Compound A32** is dehydrated, as shown in the  
 8 example by treatment with (methoxycarbonyl  
 9 sulfamoyl)triethylammonium hydroxide (*Burgess* reagent) to yield a  
 10 mixture of ethyl (E)-4-[2-(5,6-dihydro-5,5-dimethyl-8-  
 11 (carbethoxymethyl)naphthalen-2-yl)ethenyl]benzoate (**Compound A33a**),  
 12 and ethyl (E)-4-[2-(5,6-dihydro-5,5-dimethyl-8(7H)-*anti*  
 13 (carbethoxymethylidenyl)-naphthalen-2-yl)ethenyl]benzoate (**Compound**  
 14 **A33b**). **Compound A33a** is within the scope of **Formula 6**, and  
 15 **Compound A33b** is within the scope of **Formula 3**.



Reaction Scheme 6



Reaction Scheme 6 (continued)

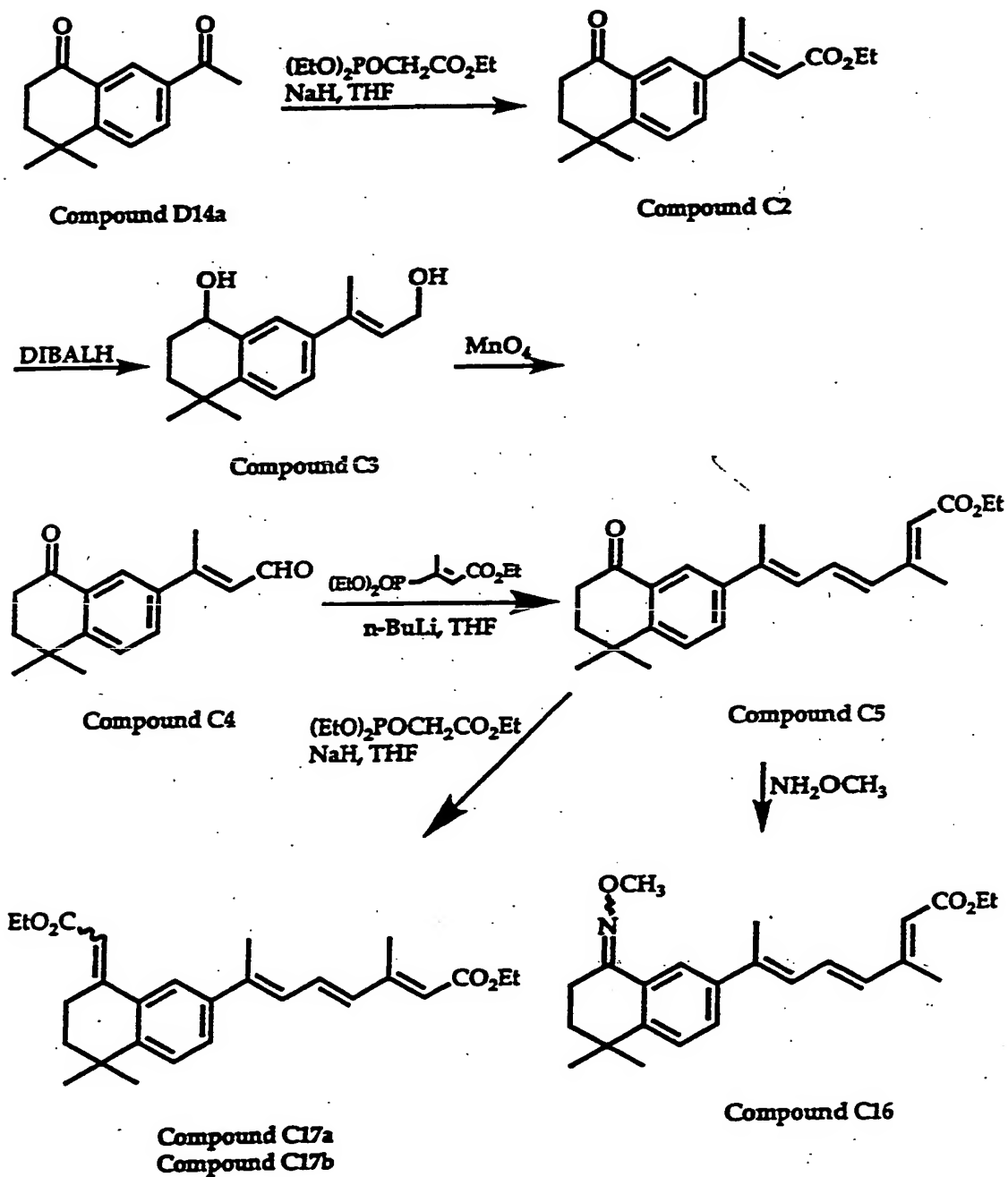


1       **Reaction Scheme 6** provides examples for the synthesis of  
 2   compounds of the invention where in accordance with **Formulas 1 - 6**  
 3   the **Z** group is  $-(CR_1=CR_1)_x-$  and  $n'$  is 0; in other words where there is  
 4   no linking group between the tetrahydronaphthalene or  
 5   dihydronaphthalene nucleus and the  $Y(R_2)$ -A-B group. For the  
 6   synthesis of these examples the starting material is  
 7   6-bromo-1,2,3,4-tetrahydro-1,1-dimethylnaphthalene (**Compound F**)  
 8   which is reacted with *n*-butyl lithium and triisopropylborate in an aprotic  
 9   solvent such as toluene to give after hydrolysis (5,6,7,8-tetrahydro-5,5-  
 10   dimethylnaphth-2-yl)boronic acid (**Compound B13**). **Compound B13**  
 11   and related boronic acid derivatives (such as **Compound B14** in this  
 12   scheme) are suitable for coupling with a reagent having the formula  $X_3$ -  
 13    $Y(R_2)$ -A-B where  $X_3$  is halogen, and the remaining symbols are defined  
 14   as for **Formulas 1 - 6**. **Reaction Scheme 6** illustrates this coupling  
 15   reaction with ethyl 6-bromo-naphthalene-2-carboxylate in the presence  
 16   of tetrakis-triphenyl-phosphine palladium(0) to yield ethyl-6-[5,6,7,8-  
 17   tetrahydro-5,5-dimethyl-naphth-2-yl]naphthoate (**Compound B1**).  
 18   **Compound B1** of the invention is within the scope of **Formula 2**. Other  
 19   reagents corresponding to formula  $X_3$ - $Y(R_2)$ -A-B are readily available in  
 20   accordance with the chemical literature and/or can be obtained in  
 21   accordance with state-of-the-art synthetic methodology. Examples for  
 22   such other reagents are ethyl 4-bromobenzoate and ethyl 2-  
 23   bromopyridine-5-carboxylate.

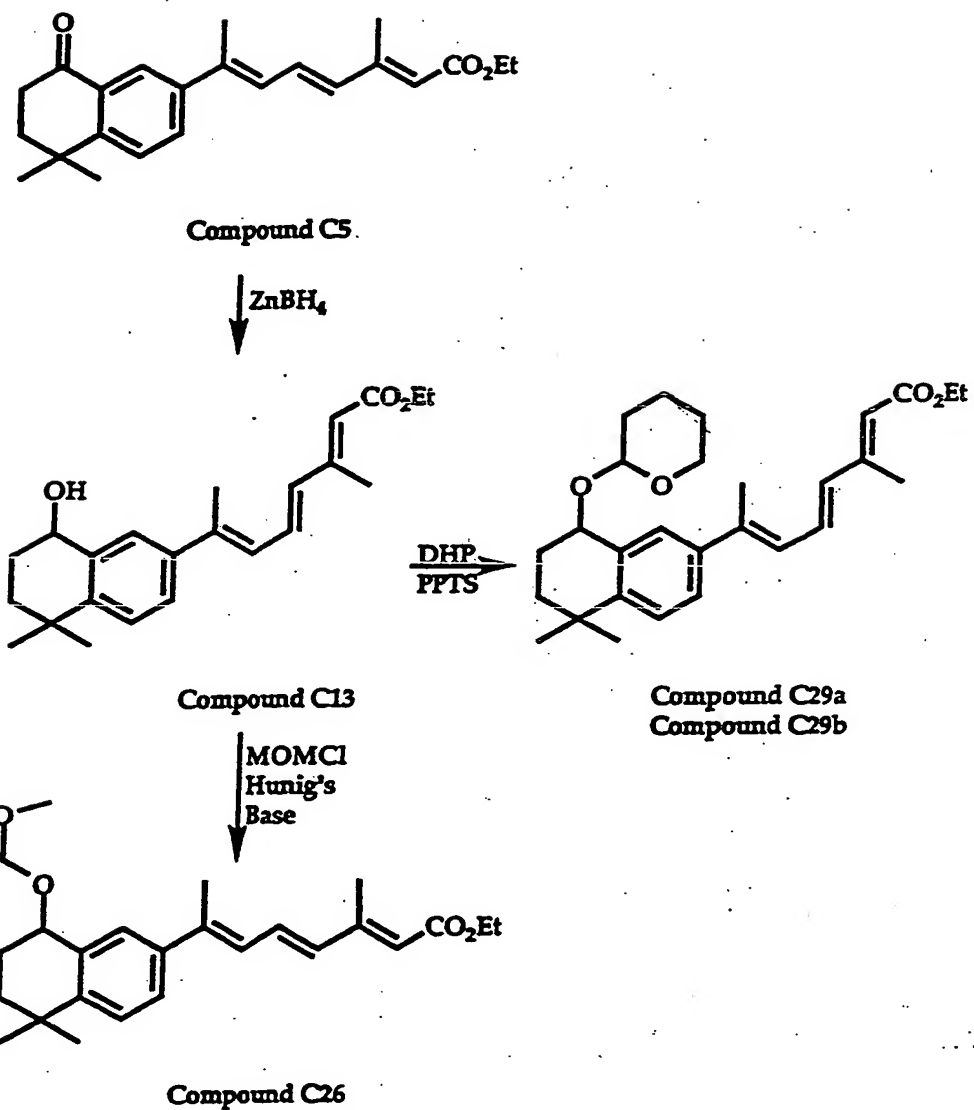
24       Continuing on with the description of **Reaction Scheme 6**, 6-  
 25   bromo-1,2,3,4-tetrahydro-1,1-dimethyl-4-hydroxynaphthalene is reacted  
 26   in the presence of base with *t*-butyldimethylsilyl chloride to provide 6-  
 27   bromo-1,2,3,4-tetrahydro-1,1-dimethyl-4-(*t*-  
 28   butyldimethylsilyloxy)naphthalene (**Compound B15**). The starting 6-

1 bromo-1,2,3,4-tetrahydro-1,1-dimethyl-4-hydroxynaphthalene can be  
2 obtained by reduction of  
3 7-bromo-3,4-dihydro-4,4-dimethylnaphthalen-1(2H)-one (Compound G).  
4 Under conditions similar to the ones described above Compound B15 is  
5 converted to the boronic acid derivative (5,5-dimethyl-8-(*t*-  
6 butyldimethylsilyloxy)-5,6,7,8-tetrahydro-naphth-2-yl)boronic acid  
7 (Compound B14). Compound B14 is then coupled with ethyl 6-bromo-  
8 naphthalene-2-carboxylate to yield ethyl 6-[5,6,7,8-tetrahydro-5,5-  
9 dimethyl-8-(*t*-butyldimethylsilyloxy)-naphth-2-yl]naphth-2-oate  
10 (Compound B3). Compound B3 is then reacted with  
11 tetrabutylammonium fluoride to remove the *t*-butyldimethylsilyl blocking  
12 group and to give ethyl 6-[5,6,7,8-tetrahydro-5,5-dimethyl-8-hydroxy-  
13 naphth-2-yl]naphth-2-oate (Compound B4). Compound B4 can be  
14 acylated to give ethyl 6-[5,6,7,8-tetrahydro-5,5-dimethyl-8-(*O*-acetyl)-  
15 naphth-2-yl]naphth-2-oate (Compound B10), or methoxymethylated with  
16 methoxymethyl chloride in the presence of base (preferably ethyl *N,N*-  
17 diisopropylamine, *Hunig's* base) to give ethyl 6-[5,6,7,8-tetrahydro-5,5-  
18 dimethyl-8-(methoxymethyloxy)-naphth-2-yl]naphth-2-oate (Compound  
19 B8), and oxidized with *N*-methyl morpholine *N*-oxide to provide ethyl -  
20 6-[5,5-dimethyl-5,6-dihydro--naphthlen-8(7H)-one-2-yl]-naphthalen-2-  
21 oate (Compound B6). Compounds B8 and B10 of the invention are  
22 within the scope of Formula 1, whereas Compound B6 is within the  
23 scope of Formula 2. Compound B6 can be converted into the *O*-  
24 methyloxime (ethyl 6-[5,5-dimethyl-5,6-dihydro--naphthlen-8(7H)-*anti*-  
25 (*O*-methyl-oxime)-2-yl]-naphthalen-2-oate (Compound B11) not shown  
26 in the scheme) and into other derivatives such as oximes, imines,  
27 hydrazones and the like, as is described above in connection with  
28 Reaction Scheme 2. Further derivatives of Compound B6 (and of

1 analogous compounds) wherein the 8-oxo function of the molecule is  
2 modified can be obtained in accordance with the general synthetic  
3 methodology described in this specification. For example the  
4 trifluoromethylsulfonyl (triflate) derivative can be obtained in analogy to  
5 the reaction leading to Compound A9 as described in Reaction Scheme  
6 2 , and the trifluoromethylsulfonyl (triflate) derivative is reacted with  
7 the reagents  $R_{14}Me$  to provide compounds of Formula 6.



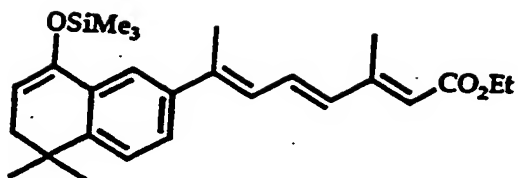
Reaction Scheme 7



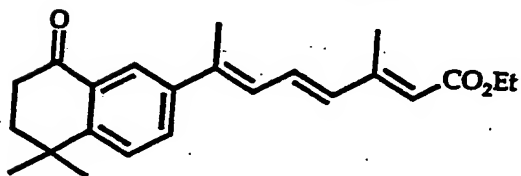
Reaction Scheme 7 (continued)

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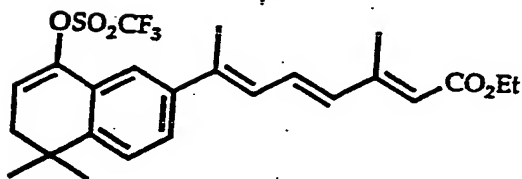
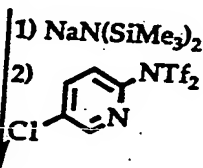
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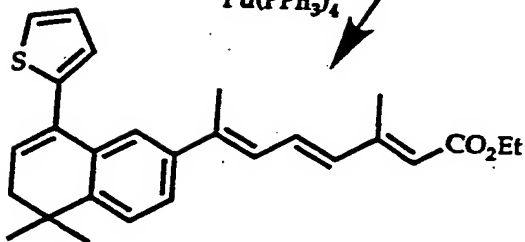
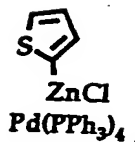
Compound C28



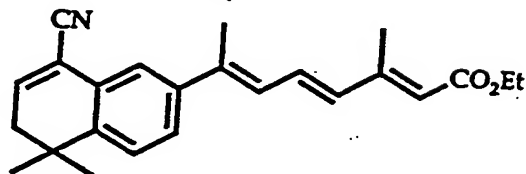
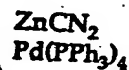
Compound C5



Compound C14



Compound C15



Compound C21

Reaction Scheme 7 (end)

1 ] Reaction Scheme 7 discloses a preferred example of a synthetic  
 2 route leading to compounds of the invention where with reference to  
 3 Formulas 1 - 6 the symbol Z represents  $-(CR_1=CR_1)_{n'}$ , where  $n'$  is 3,  
 4 and there is no  $Y(R_2)$  group. Thus, 4,4-dimethyl-7-acetyl-1,2,3,4-  
 5 tetrahydronaphthalen-1(2H)-one (Compound D14a) is reacted in a  
 6 *Horner Emmons* type reaction with triethylphosphonoacetate in the  
 7 presence of sodium hydride in an ether type solvent such as  
 8 tetrahydrofuran. Conditions of the *Horner Emmons* reaction are well  
 9 known in the art, and it is also well known that usually a related *Wittig*  
 10 type reaction can also be employed using a trialkylphosphonium reagent  
 11 instead of the phosphonate reagent, to yield the same products as is  
 12 obtained in the *Horner Emmons* reaction. The product of the *Horner*  
 13 *Emmons* reaction in this example is ethyl 3-[4,4-dimethyl-1,2,3,4,-  
 14 tetrahydronaphthalen-1(2H)one-7-yl]but-2(E)-enoate (Compound C2)  
 15 which is reduced with diisobutyl aluminum hydride to provide 3-[1-  
 16 hydroxy-4,4-dimethyl-1,2,3,4,-tetrahydronaphthalen-7-yl]but-2(E)-en-1-ol  
 17 (Compound C3). Compound C3 is oxidized back to the aldehyde and  
 18 ketone "stage" with manganese dioxide to give 3-[4,4-dimethyl-1,2,3,4,-  
 19 tetrahydronaphthalen-1(2H)one-7-yl]but-2(E)-en-al (Compound C4).  
 20 Compound C4 is subjected to yet another *Horner Emmons* type reaction  
 21 with diethyl-(E)-3-ethoxycarbonyl-2-methylallylphosphonate (available  
 22 from the chemical literature; see: *Vuligunda et al. Biorganic Medical*  
 23 *Chemistry Letters*, (1996) 6 p213-218) in tetrahydrofuran in the  
 24 presence of *n*-butyl lithium, to yield ethyl 7-[4,4-dimethyl-3,4,-  
 25 dihydronaphthalen-1(2H)one-7-yl]-3,7-dimethyl-hept-2(E), 4(E),  
 26 6(E)trienoate (Compound C5).

27 Compound C5 of the invention is within the scope of Formula 2, and  
 28 is also readily converted to further compounds of the invention in

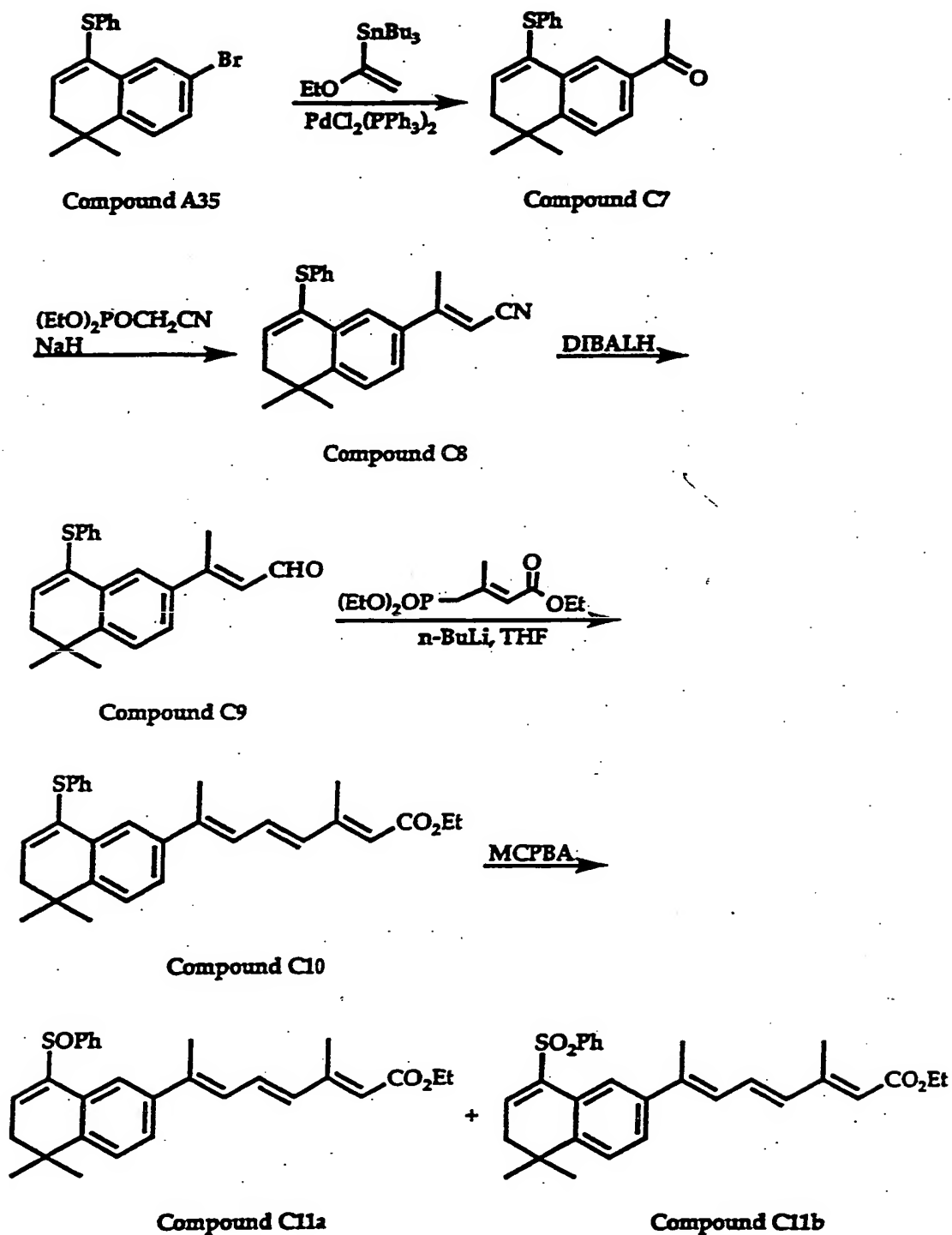
1 accordance with the generic principles disclosed in this specification.  
 2 Several examples of reactions which provide further compounds of the  
 3 invention using **Compound C5** as the starting material are shown in  
 4 **Reaction Scheme 7**. These reactions are described in less detail to the  
 5 extent that they are of the types which have been described above. Thus,  
 6 the "oxo" compound ethyl 7-[4,4-dimethyl-3,4,-dihydronaphthalen-  
 7 1(2H)one-7-yl]-3,7-dimethyl-hept-2(E), 4(E), 6(E)trienoate (**Compound**  
 8 **C5**) is saponified to yield the free acid (not shown in the scheme), is  
 9 converted to the *O*-methyl-oxime derivative (**Compound C16**); to ethyl  
 10 7-[4,4-dimethyl-3,4-dihydro-1-(trimethylsiloxy)-naphth-7-yl]3,7-dimethyl-  
 11 hepta-2(E),4(E),6(E)-trienoate (1-trimethylsilyloxy derivative  
 12 **Compound C28**); and to ethyl 7-[4,4-dimethyl-3,4,-dihydronaphthalen-1-  
 13 trifluoromethylsulfonyloxy-7-yl]-3,7-dimethyl-hept-2(E), 4(E),  
 14 6(E)trienoate ("triflate", **Compound C14**). **Compounds C14** and **C28**  
 15 are within the scope of **Formula 5**, whereas **Compound C16** is within  
 16 the scope of **Formula 4**. Another *Horner Emmons* type reaction of  
 17 **Compound C5** which leads to compounds within the scope of **Formula 3**  
 18 (**Compounds 17a** and **17B**) is shown in the scheme.

19 In the examples shown in **Reaction Scheme 7** the "oxo" compound  
 20 ethyl 7-[4,4-dimethyl-3,4,-dihydronaphthalen-1(2H)one-7-yl]-3,7-  
 21 dimethyl-hept-2(E), 4(E), 6(E)trienoate (**Compound C5**) is also  
 22 reduced with  $\text{ZnBH}_4$  to yield the corresponding secondary alcohol,  
 23 ethyl 7-[4,4-dimethyl-1,2,3,4,-tetrahydronaphthalen-1-hydroxy-7-yl]-3,7-  
 24 dimethyl-hept-2(E), 4(E), 6(E)trienoate (**Compound C13**). **Compound**  
 25 **C13** is reacted with chloromethylmethyl ether to give (-/+ )ethyl 7-[4,4-  
 26 dimethyl-1,2,3,4-tetrahydro-1-(*O*-methoxymethyl)-naphth-7-yl]3,7-  
 27 dimethyl-hepta-2(E),4(E),6(E)-trienoate (**Compound C26**); alternatively  
 28 it is reacted with 3,4-dihydro-2H-pyran in methylene chloride in the



1 presence of *p*-toluene sulfonic acid (*p*-TsOH) to give the diastereomeric  
2 dihydropyranoxy derivatives, (+/-)ethyl 7-[4,4-dimethyl-1,2,3,4-  
3 tetrahydro-1(RS)-(2'(RS)-  
4 tetrahydropyranoxy)-naphth-2-yl]-3,7-dimethyl-hepta-2(E),4(E),6(E)-  
5 trienoate (Compound C29a) and (+/-)ethyl 7-[4,4-dimethyl-1,2,3,4-  
6 tetrahydro-1(RS)-(2'(SR)-tetrahydropyranoxy)-naphth-2-yl]-3,7-dimethyl-  
7 hepta-2(E),4(E),6(E)-trienoate (Compound C29b). Compounds C13,  
8 C26, C29a and C29b of the invention are within the scope of Formula  
9 1.

10 The trifluoromethylsulfonate (triflate) derivative Compound C14 is  
11 itself an important starting material for the syntheses of several  
12 compounds of the invention within the scope of Formula 6; among  
13 these the preparations of ethyl 7-[4,4-dimethyl-3,4,-dihydronaphthalen-1-  
14 (2-thienyl)-7-yl]-3,7-dimethyl-hept-2(E), 4(E), 6(E)trienoate (Compound  
15 C15) and of ethyl 7-[4,4-dimethyl-3,4,-dihydronaphthalen-1-cyano-7-yl]-  
16 3,7-dimethyl-hept-2(E), 4(E), 6(E)trienoate (Compound 21) are  
17 illustrated in the reaction scheme.



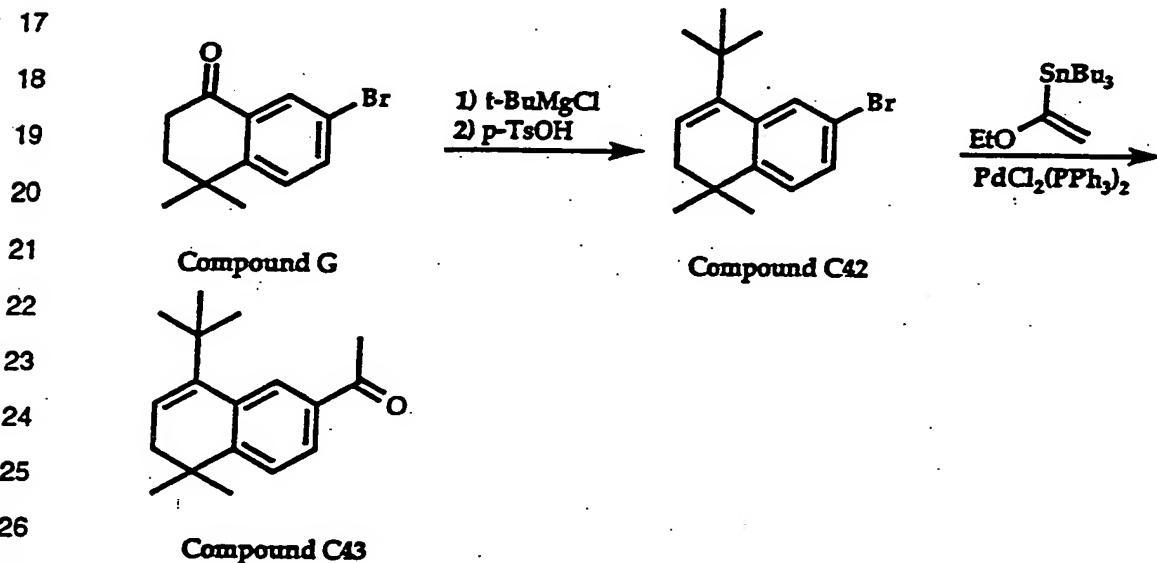
Reaction Scheme 8

1       **Reaction Scheme 8** discloses other examples for synthesizing  
 2       preferred compounds of the invention where with reference to **F** formula  
 3       **5** the symbol **Z** represents  $-(CR_1=CR_1)_{n'}$ , where  $n'$  is 3, and there is no  
 4       **Y(R<sub>2</sub>)** group. The starting compound for the series of reactions shown  
 5       in this scheme is 4,4-dimethyl-7-bromo-1-phenylthio-3,4-  
 6       dihydronaphthalene (**Compound A35**) which can be obtained as shown  
 7       in **Reaction Scheme 3**. Thus, referring now to **Reaction Scheme 8**,  
 8       **Compound A35** is reacted with 1-ethoxyvinyltributyltin (EVTB, available  
 9       from Aldrich Chemical Co.) in the presence of  
 10       bis(triphenylphosphine)palladium(II)chloride in tetrahydrofuran to  
 11       provide, after acid work-up, 4,4-dimethyl-7-acetyl-1-phenylthio-3,4-  
 12       dihydronaphthalene (**Compound C7**). **Compound C7** is subjected to a  
 13       *Horner Emmons* reaction (as described above) with  
 14       diethylcyanomethylphosphonate (available from Aldrich Chemical Co.)  
 15       to provide 3-[4,4-dimethyl-1-phenylthio-3,4-dihydronaphthalen-7-yl]but-  
 16       2-en(E)-nitrile (**Compound C8**). **Compound C8** is reduced with  
 17       diisobutyl aluminium hydride to provide the corresponding aldehyde, 3-  
 18       [4,4-dimethyl-1-phenylthio-3,4-dihydronaphthalen-7-yl]but-2-en(E)-  
 19       aldehyde (**Compound C9**). **Compound C9** is subjected to still another  
 20       *Horner Emmons* reaction with the reagent diethyl-(E)-3-ethoxycarbonyl-  
 21       2-methylallylphosphonate to yield ethyl 7-[4,4-dimethyl-1-phenylthio-  
 22       3,4-dihydronaphthalen-7-yl]-3,7-dimethyl-hept-2(E), 4(E), 6(E)trienoate  
 23       (**Compound C10**). **Compound C10** of the invention is within the scope  
 24       of **Formula 5**.

25       In other preferred examples not shown in the schemes but described  
 26       in the **Specific Examples**, a sequence of reaction which is analogous to  
 27       the above-described reactions of **Reaction Scheme 8** is conducted,  
 28       starting with 7-bromo-1(2H)-(propyliden-2-yl)-3,4-dihydro-4,4-

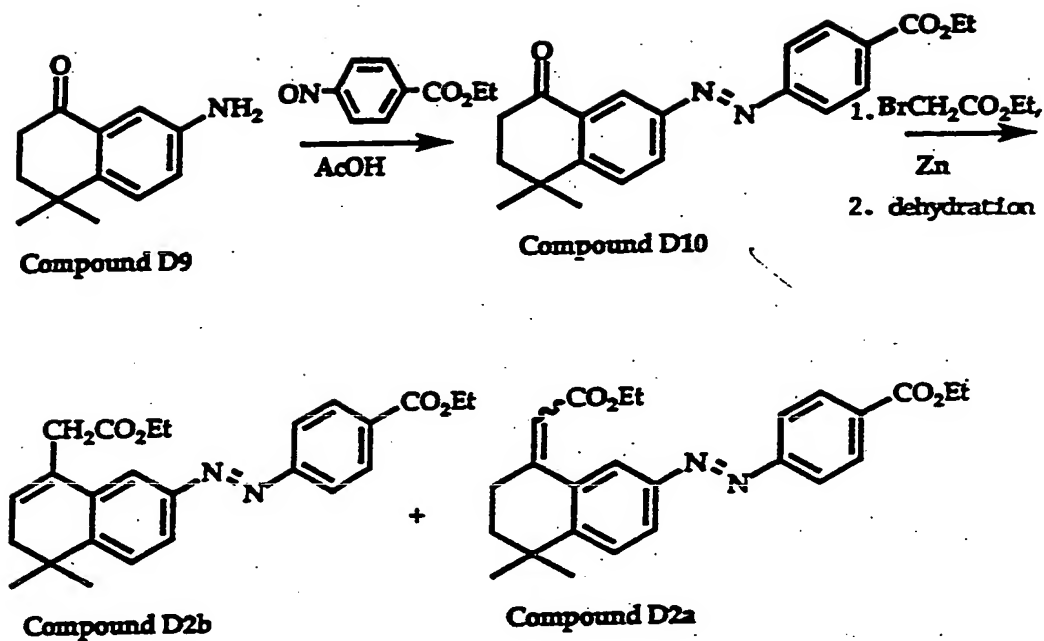
1 dimethylnaphthalene (Compound A37), or with 7-bromo-1(2H)-  
 2 (phenylbenzylidenyl)-3,4-dihydro-4,4-dimethylnaphthalen (Compound  
 3 C37) to provide further examples for compounds of the invention, such  
 4 as ethyl-7-[1(2H)-(propyliden-2-yl)-3,4-dihydro-4,4-dimethyl-naphthalen-  
 5 7-yl]-3,7-dimethyl-hept-2(E),4(E),6(E)-trienoate (Compound C36) and  
 6 ethyl 7-[4,4-dimethyl-3,4-dihydro-1(2H)-phenylbenzylidenyl)-naphth-7-  
 7 yl]-3,7-dimethyl-hepta-2(E),4(E),6(E)-trienoate (Compound C41).  
 8 Compounds C36 and C41 of the invention are within the scope of  
 9 Formula 3.

10 Compound C10 is converted by oxidation with *meta*-  
 11 chloroperoxybenzoic acid to the corresponding sulfone and sulfoxide,  
 12 ethyl 7-[4,4-dimethyl-1-phenylsulfonyl-3,4,-dihydronaphthalen-7-yl]-3,7-  
 13 dimethyl-hept-2(E), 4(E), 6(E)trienoate (Compound C11a) and ethyl 7-  
 14 [4,4-dimethyl-1-phenylsulfoxide-3,4,-dihydronaphthalen-7-yl]-3,7-  
 15 dimethyl-hept-2(E), 4(E), 6(E)trienoate (Compound C11b), which are  
 16 also within the scope of Formula 5.

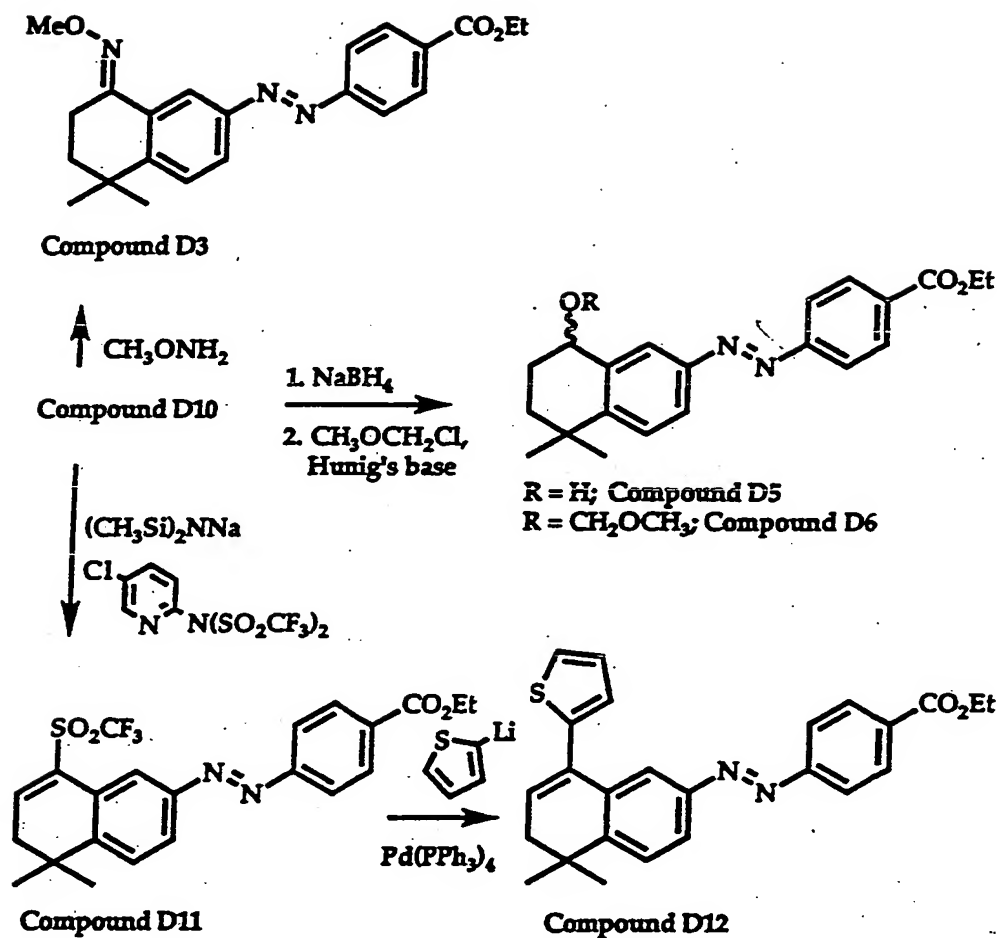


Reaction Scheme 9

1        **Reaction Scheme 9** discloses the preferred method of synthesis of a  
2        starting material from which certain examples for compounds of the  
3        invention within the scope of **Formula 6** are preferably made. In  
4        accordance with this scheme  
5        7-bromo-3,4-dihydro-4,4-dimethylnaphthalen-1(2H)-one (**Compound G**)  
6        is reacted with *t*-butylmagnesium chloride in tetrahydrofuran in the  
7        presence of 1,3-dimethyl-3,4,5,6-tetrahydro-2(H)-pyrimidinone (DMPU).  
8        Thereafter, the resulting intermediate tertiary alcohol is heated in the  
9        presence of acid (*p*-toluenesulfonic acid) to give 7-bromo-1-(1,1-  
10       dimethylethyl)-3,4-dihydro-4,4-dimethylnaphthalene (**Compound C42**).  
11       **Compound C42** is reacted with 1-ethoxyvinyltributyltin (EVTB) in the  
12       presence of Pd(0) catalyst to yield after acidic work-up 7-acetyl-1-(1,1-  
13       dimethylethyl)-3,4-dihydro-4,4-dimethylnaphthalene (**Compound C43**).  
14       **Compound C43** is subjected to a sequence of reactions of the type  
15       described above in connection with **Reaction Scheme 8**, starting with a  
16       *Horner Emmons* reaction with diethyl cyanomethylphosphonate, to  
17       eventually provide ethyl 7-[4,4-dimethyl-3,4-dihydro-1-(1,1-  
18       dimethylethyl)-naphth-7-yl]-3,7-dimethyl-hepta-2(E),4(E),6(E)-trienoate  
19       (**Compound C46**). **Compound C46** of the invention is within the scope  
20       of **Formula 6**.



Reaction Scheme 10



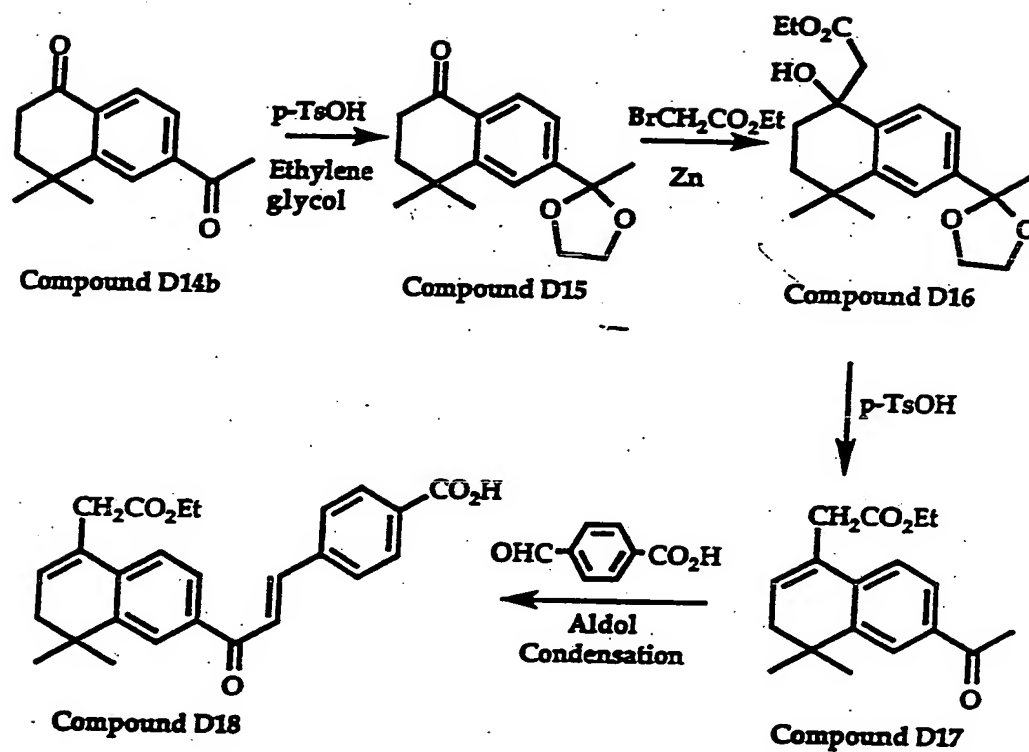
Reaction Scheme 10 (continued)

1       **Reaction Scheme 10** discloses a preferred synthetic route to certain  
 2       exemplary compounds of the invention where, with reference to  
 3       **Formulas 1 - 6** the **Z** group is -N=N- (azo) moiety. For the examples  
 4       shown in this scheme the starting compound is 3,4-dihydro-4,4-dimethyl-  
 5       7-amino-naphthalen-1(2H)-one (**Compound D9**). **Compound D9** is  
 6       coupled with a nitroso compound of the formula ON-Y(R<sub>2</sub>)-A-B, which  
 7       in the herein shown example is ethyl 4-nitrosobenzoate (available in  
 8       accordance with the chemical literature; see *Kagechika et al. J. Med.*  
 9       *Chem.* (1989) 32, 1098-1108). The coupling reaction is conducted in  
 10      glacial acetic acid and yields ethyl 4-[(5,6-dihydro-5,5-dimethyl-8(7H)-  
 11      one-naphthalen-2-yl)azo]-benzoate (**Compound D10**). **Compound D10**  
 12      of the invention is within the scope of **Formula 2**. **Compound D10** is  
 13      reacted in a *Reformatsky* reaction with ethyl bromoacetate to provide  
 14      (+/-) ethyl 4-[(5,5-dimethyl-8-hydroxy-8-carbethoxymethyl-5,6,7,8-  
 15      tetrahydronaphth-2-yl)azo]benzoate (**Compound D1**). **Compound D1** of  
 16      the invention is within the scope of **Formula 1**. Dehydration of  
 17      **Compound D1** with dicyclohexylcarbodiimide and cuprous chloride in  
 18      benzene provides the isomeric compounds ethyl 4-[(5,5-dimethyl-8(7H)-  
 19      (carbethoxymethylidenyl)-5,6-dihydronaphthalen-2-yl)azo]benzoate  
 20      (**Compound D2a**) and ethyl 4-[(5,5-dimethyl-8-(carbethoxymethyl)-5,6-  
 21      dihydronaphthalen-2-yl)azo]benzoate (**Compound D2b**). **Compound**  
 22      **D2a** of the invention is within the scope of **Formula 3**, and **Compound**  
 23      **D2b** is within the scope of **Formula 6**.

24      The "oxo" compound ethyl 4-[(5,6-dihydro-5,5-dimethyl-8(7H)-one-  
 25      naphthalen-2-yl)azo]-benzoate (**Compound D10**) serves as starting  
 26      material for reactions which lead to further compounds of the invention  
 27      in accordance with synthetic methodology that has been described  
 28      above. More particularly, in the examples shown in **Reaction Scheme**



1    10 Compound D10 is converted into the *O*-methyl oxime derivative ethyl  
2    4-[(8(7H)-*anti*-(*O*-methyl oxime)-5,5-dimethyl-5,6-dihydronaphthalen-2-  
3    yl)azo]benzoate (Compound D3), into the "triflate" ethyl 4-[(5,6-  
4    dihydro-5,5-dimethyl-8-(trifluoromethylsulfonyl)oxy-naphthalen-2-yl)azo]-  
5    benzoate (Compound D11) and is reduced to the secondary alcohol (+/-  
6    ) ethyl 4-[(5,5-dimethyl-8-hydroxy-5,6,7,8-tetrahydronaphthalen-2-  
7    yl)azo]benzoate (Compound D5). The *O*-methyl oxime derivative  
8    (Compound D3) of the invention is within the scope of Formula 4, the  
9    "triflate" Compound D11 is in the scope of Formula 5, whereas the  
10   secondary alcohol Compound D5 is within the scope of Formula 1.  
11   The secondary alcohol, Compound D5 is further converted into the  
12   methoxymethyl derivative (+/-) ethyl 4-[(5,5-dimethyl-8-  
13   (methoxymethoxy)-5,6,7,8-tetrahydronaphthalen-2-yl)azo]benzoate  
14   (Compound D6) within the scope of Formula 1, and the "triflate" is  
15   reacted with thienyl lithium in the presence of ZnCl<sub>2</sub> and Pd(0) catalyst  
16   to provide ethyl 4-[(5,5-dimethyl-8-(2-thienyl)-5,6-dihydronaphthalen-2-  
17   yl)azo]benzoate (Compound D12).



Reaction Scheme 11

1 Referring now to Reaction Scheme 11 a preferred example for the  
2 synthesis of those compounds of the invention is described where, with  
3 reference to Formulas 1 - 6 the Z group is  $-\text{CO}-\text{CR}_1=\text{CR}_1-$ . As it will  
4 become apparent from the reaction scheme, these compounds are  
5 obtained as a result of an aldol condensation between an appropriately  
6 substituted tetrahydro or dihydronaphthalene ketone derivative and an  
7 aldehyde of the formula  $\text{OCH}-\text{Y}(\text{R}_2)\text{A}-\text{B}$ . In the example shown in  
8 Reaction Scheme 11 the exocyclic ketone function of 3,4-dihydro-4,4-  
9 dimethyl-6-acetyl-naphthalen-1(2H)-one (Compound D14b) is reacted  
10 with ethylene glycol and acid to provide 6-(2-methyl-1,3-dioxolan-2-yl)-  
11 3,4-dihydro-4,4-dimethylnaphthalen-1(2H)-one (Compound D15) where  
12 one ketone function is protected. Compound D15 is then reacted with  
13 ethyl bromoacetate in a *Reformatsky* reaction to give (+/-) 6-(2-methyl-  
14 1,3-dioxolan-2-yl)]-1,2,3,4-tetrahydro-4,4-dimethyl-1-hydroxy-1-  
15 (carboethoxymethyl)-naphthlene (Compound D16). Treatment with acid  
16 of Compound D16 removes the 1,3-dioxolanyl protecting group and also  
17 introduces a double bond into the tetrahydronaphthalene nucleus, thus  
18 providing 3,4-dihydro-4,4-dimethyl-1-(carbethoxymethyl)-6-acetyl-  
19 naphthalene (Compound D17).

20 An alternate method for obtaining dihydronaphthalene compounds  
21 having the 6-acetyl substituent and a substituent in the 1-position  
22 (attached to the vinylic carbon) is to react Compound D15 with sodium  
23 bis(trimethylsilyl)amide and 2-[*N,N*-bis(trifluorometh-  
24 ylsulfonyl)amino]-5-chloropyridine in an inert ether type solvent, such as  
25 tetrahydrofuran, at low temperatures ( $-78^\circ\text{C}$  and  $0^\circ\text{C}$ ). As noted above  
26 in connection with an analogous "triflate" forming reaction, this reaction  
27 proceeds through a sodium salt intermediate which is usually not  
28 isolated. The overall reaction results in a trifluoromethylsulfonyloxy

1 derivative, which is thereafter reacted with an organometal derivative,  
 2 again in analogy to the preceding description of synthesizing compounds  
 3 of Formula 6 from the "triflate" derivatives.

4 Returning now to the description of Reaction Scheme 11, Compound  
 5 D17 is reacted with 4-carboxybenzaldehyde in an aldol condensation  
 6 reaction to give ethyl (E)-4-[3-(3,4-dihydro-4,4-dimethyl-1-  
 7 (carbethoxymethyl)-naphthalen-6-yl)-prop-1-en-3-one]benzoate  
 8 (Compound D18). The just described aldol condensation reaction is  
 9 conducted in the presence of base in an alcoholic solvent. Preferably,  
 10 the reaction is conducted in methanol or ethanol in the presence of  
 11 sodium hydroxide. Those skilled in the art will recognize the aldol  
 12 condensation reaction of this example as a Claisen-Schmidt reaction.  
 13 (See March: Advanced Organic Chemistry: Reactions, Mechanisms, and  
 14 Structure, pp 694 695 McGraw Hill (1968). Examples of other reagents  
 15 analogous to 4-carboxybenzaldehyde and suitable for the condensation  
 16 reaction to introduce heterocyclic Y(R<sub>2</sub>) groups into the compounds of  
 17 the present invention 1) are: 5-carboxypyridine-2-carboxaldehyde,  
 18 4-carboxypyridine-2-carboxaldehyde,  
 19 4-carboxythiophene-2-carboxaldehyde,  
 20 5-carboxythiophene-2-carboxaldehyde, 4-carboxyfuran-2-carboxaldehyde,  
 21 5-carboxyfuran-2-carboxaldehyde, 4-carboxyacetophenone,  
 22 2-acetylpyridine-5-carboxylic acid, 2-acetylpyridine-4-carboxylic acid,  
 23 2-acetyl-thiophene-4-carboxylic acid, 2-acetylthiophene-5-carboxylic acid,  
 24 2-acetylfuran-4-carboxylic acid, and 2-acetylfuran-5-carboxylic acid. The  
 25 latter compounds are available in accordance with the chemical  
 26 literature; see for example Decroix et al., J. Chem. Res.(S), 1978, 4, 134;  
 27 Dawson et al., J. Med. Chem., 1983, 29, 1282; and Queguiner et al.,  
 28 Bull Soc. Chimique de France, 1969, No. 10, pp 3678-3683. Compound

1 D18 of the invention is within the scope of Formula 6.

2 To obtain further preferred examples of the compounds of the  
3 invention where the Z group is  $-\text{CO}-\text{CR}_1=\text{CR}_1-$  the aldol condensation  
4 reaction shown in Reaction Scheme 11 is performed on the following  
5 compounds:

6 3,4-dihydro-4,4-dimethyl-6-acetyl-1-(1,1-dimethylethyl)naphthalene  
7 (Compound D19);

8 6-Acetyl-1(2H)-(propyliden-2-yl)-3,4-dihydro-4,4-dimethylnaphthalene  
9 (Compound D22);

10 (+/-) 1-(methoxymethoxy)-6-acetyl-1,2,3,4-tetrahydro-4,4-dimethyl-  
11 naphthalene (Compound D26); and

12 6-Acetyl-1(2H)-(O-methyl oxime)-3,4-dihydro-4,4-  
13 dimethylnaphthalene (Compound D28)

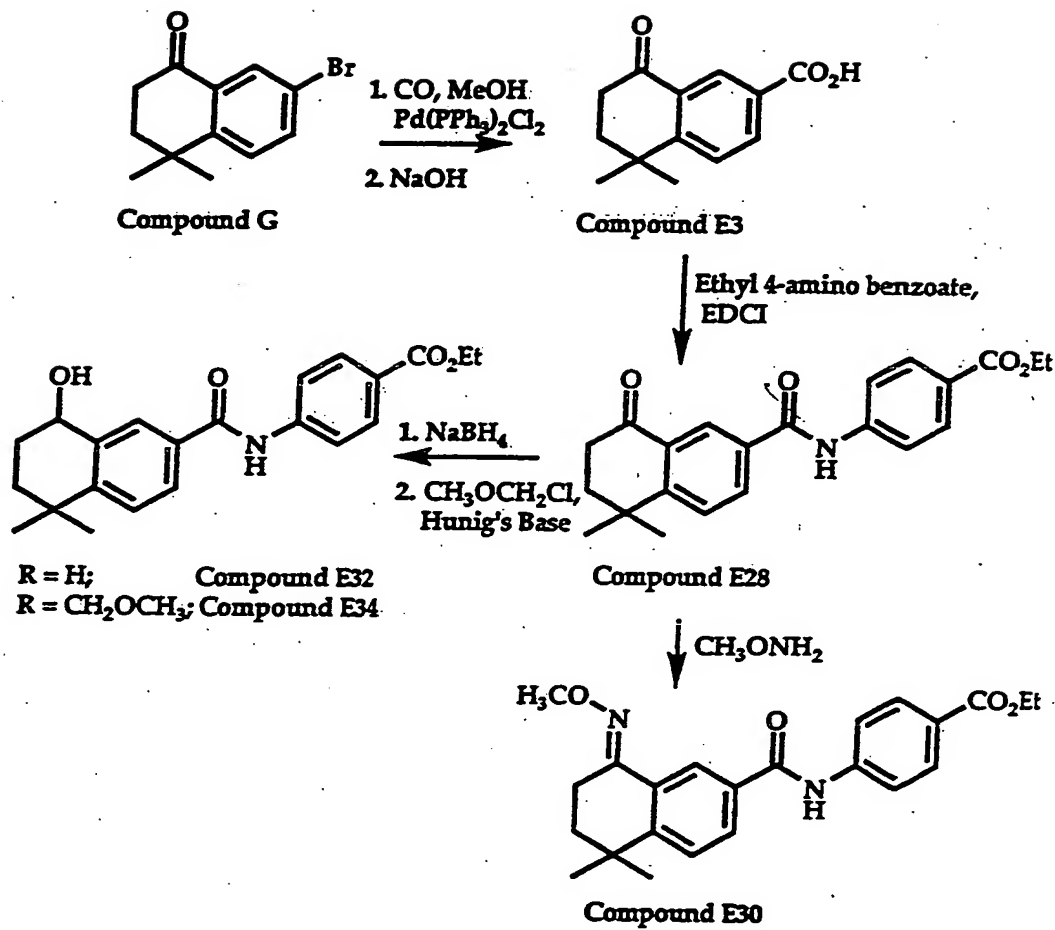
14 to provide respectively the following examples of compounds of the  
15 invention:

16 (E)-4-[3-(3,4-dihydro-4,4-dimethyl-1-(1,1-dimethyl-ethyl)naphth-6-yl)-  
17 prop-1-en-3-one]benzoic acid (Compound D20, Formula 6);

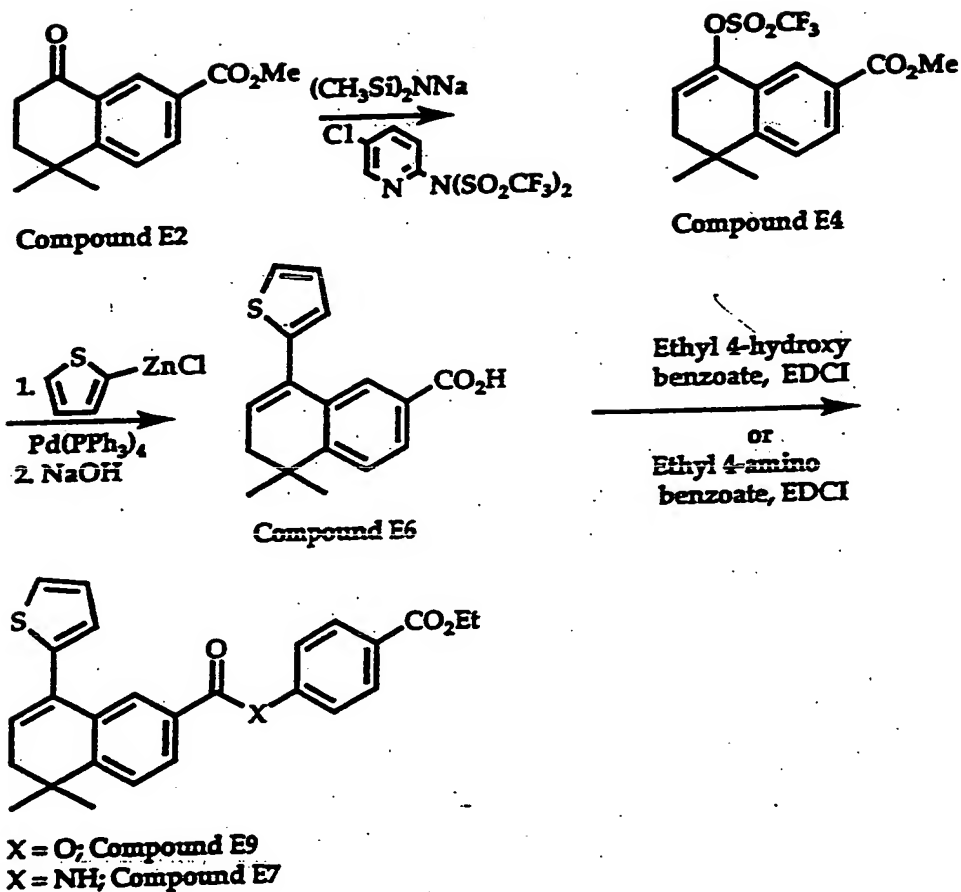
18 (E)-4[3-{1(2H)-(propyliden-2-yl)-3,4-dihydro-4,4-dimethylnaphthalen-  
19 6-yl}-prop-1-en-3-one]benzoic acid (Compound D23, Formula 3);

20 (E)-4-[3-(1,2,3,4-tetrahydro-4,4-dimethyl-1-(methoxymethoxy)-  
21 naphthalen-6-yl)-prop-1-en-3-one]benzoic acid (Compound D27,  
22 Formula 1), and

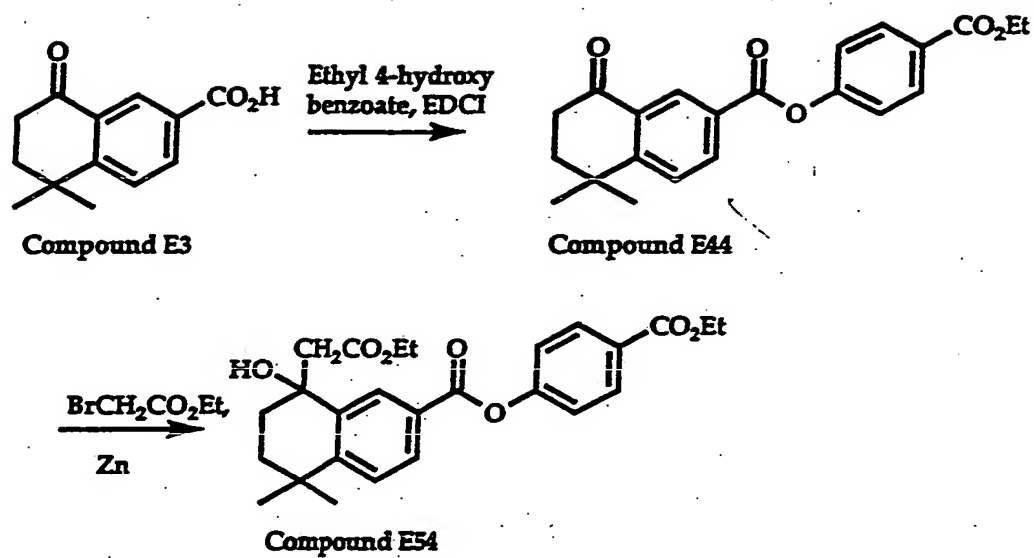
23 (E)-4[3-{1(2H)-(O-methyl oxime)-3,4-dihydro-4,4-  
24 dimethylnaphthalen-6-yl}-prop-1-en-3-one]benzoic acid (Compound  
25 D29, Formula 4).



Reaction Scheme 12



Reaction Scheme 12 (continued)



Reaction Scheme 12 (end)



1        **Reaction Scheme 12** discloses the presently preferred methods for  
2        synthesizing preferred examples of compounds of the invention where  
3        with reference to **Formulas 1 - 6** the **Z** group is -COO- or -CONH-. As  
4        is shown in the scheme,  
5        7-bromo-3,4-dihydro-4,4-dimethylnaphthalen-1(2H)-one (**Compound G**)  
6        is reacted with carbon monoxide in the presence of palladium(II)-  
7        bis(triphenylphosphine)chloride, 1,3-bis(diphenylphosphino)-propane,  
8        DMSO, methanol and triethylamine to obtain the corresponding  
9        carboxylic acid methyl ester, methyl 5,5-dimethyl-5,6-dihydro-  
10       naphthalen-8(7H)-one-2-carboxylate (**Compound E2**), which is thereafter  
11       saponified to provide 5,5-dimethyl-5,6-dihydro-naphthalen-8(7H)-one-2-  
12       carboxylic acid (**Compound E3**). **Compound E3** is a free carboxylic acid  
13       which is reacted either with compounds of the formula  $H_2N-Y(R_2)-A-B$   
14       to provide compounds of the invention where **Z** is -CONH-, or with  
15       compounds of the formula  $HO-Y(R_2)-A-B$  to provide compounds of the  
16       invention where **Z** is -COO-. Those skilled in the art will recognize  
17       that these compounds of the invention are amide and ester compounds,  
18       respectively. Generally speaking several known methods for amide and  
19       ester formation may be employed for their synthesis from **Compound E3**  
20       or analogous carboxylic acid compounds. For example, **Compound E3**  
21       or analogous carboxylic acid compounds can be converted into the acid  
22       chloride by known methods and thereafter reacted with the amines or  
23       esters of formula  $H_2N-Y(R_2)-A-B$  or formula  $HO-Y(R_2)-A-B$   
24       respectively. The presently preferred method for synthesis, however  
25       utilizes the reagents 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide  
26       hydrochloride (EDCI) and 4-*N,N*-dimethylaminopyridine in an aprotic  
27       solvent for the amide or ester formation. Those skilled in the art will  
28       also recognize that the compounds of formula  $H_2N-Y(R_2)-A-B$  and

1 formula HO-Y(R<sub>2</sub>)-A-B are aromatic or heteroaromatic amines or  
2 hydroxyl derivatives, which can be obtained in accordance with the  
3 state-of-the-art.

4 Referring now back to Reaction Scheme 12 that describes certain  
5 preferred specific examples, 5,5-dimethyl-5,6-dihydro-naphthalen-8(7H)-  
6 one-2-carboxylic acid (Compound E3) is reacted in the presence of 1-(3-  
7 dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) and 4-  
8 (dimethylamino)pyridine in methylene chloride to give ethyl 4-[(5,5-  
9 dimethyl-8(7H)-one-5,6-dihydronaphthalen-2-yl)carboxamido]benzoate  
10 (Compound 28). Compound 28 of the invention is in the scope of  
11 Formula 2. Reaction Scheme 12 discloses its conversion by reactions of  
12 the type described above, to ethyl 4-[(5,5-dimethyl-8(7H)-*anti*-(O-  
13 methyloxime)-5,6-dihydronaphthalen-2-yl)carboxamido]benzoate  
14 (Compound E30, Formula 4) and (+/-) 4-[(5,5-dimethyl-8-hydroxy-  
15 5,6,7,8-tetrahydronaphthalen-2-yl)carboxamido]benzoic acid (Compound  
16 E32, Formula 1). Compound E32 is converted to the methoxymethyl  
17 derivative (+/-) ethyl 4-[(5,5-dimethyl-8-(O-methoxymethyl)-5,6,7,8-  
18 tetrahydronaphthalen-2-yl)carboxamido]benzoate (Compound E34)  
19 within the scope of Formula 1. Each of these amide compounds can  
20 have their respective COOEt group saponified to provide the free  
21 carboxylic acid or its salt.

22 Referring still to Reaction Scheme 12, methyl 5,5-dimethyl-5,6-  
23 dihydro-naphthalen-8(7H)-one-2-carboxylate (Compound E2) is  
24 converted, under conditions described above for analogous reactions,  
25 into the trifluoromethylsulfonyl ("triflate") derivative, methyl 5,5-  
26 dimethyl-5,6-dihydro-8-(trifluoromethylsulfonyl)oxy-naphthalene -2-  
27 carboxylate (Compound E4). Compound E4 serves as an important  
28 intermediate for the synthesis of compounds within the scope of

1    **Formula 6.** In the preferred examples shown in the reaction scheme,  
2    **Compound E4** is reacted with the lithium derivative of thiophene in the  
3    presence of  $\text{ZnCl}_2$  and  $\text{Pd}(0)$  catalyst to provide the thienyl substituted  
4    carboxylic acid methyl ester, (**Compound E5**). The latter compound is  
5    saponified to give 5,5-dimethyl-5,6-dihydro-8-(2-thienyl)-naphthalene-2-  
6    carboxylic acid (**Compound E6**). **Compound E6** is coupled with ethyl 4-  
7    aminobenzoate to give ethyl 4-[[[(5,5-dimethyl-5,6-dihydro-8-(2-thienyl)-  
8    naphthalen-2-yl)carboxamido]-benzoate (**Compound E7**), and with ethyl  
9    4-hydroxybenzoate to provide ethyl 4-[[[(5,5-dimethyl-5,6-dihydro-8-(2-  
10    thienyl)-naphthalen-2-yl)carbonyl]oxy]-benzoate (**Compound E9**).  
11    **Compounds E7 and E9** of the invention are within the scope of  
12    **Formula 6.**

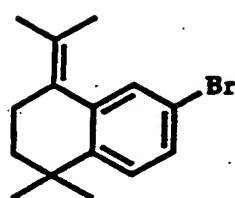
13        As it will be readily recognized in the art, the free carboxylic acid  
14    derivatives of the invention could not be obtained (or could be obtained  
15    only with difficulty) from the carbonyloxy compounds of the present  
16    invention by a process of saponification of the ester compounds such as  
17    **Compound E9**. However, the above-mentioned free carboxylic acids,  
18    such as 4-[[[(5,5-dimethyl-5,6-dihydro-8-(2-thienyl)-naphthalen-2-  
19    yl)carbonyl]oxy]-benzoic acid (**Compound E11**) can be obtained from  
20    the corresponding 2-(trimethylsilyl)ethyl esters (such as 2-  
21    (trimethylsilyl)ethyl 4-[[[(5,5-dimethyl-5,6-dihydro-8-(2-thienyl)-  
22    naphthalen-2-yl)carbonyl]oxy]-benzoate, (**Compound E10**) by treatment  
23    with tetrabutylammonium fluoride. **Compound E10** and like compounds  
24    can be obtained by coupling reactions of the type described above,  
25    utilizing, for example, 2-trimethylsilylethyl 4-hydroxybenzoate. The  
26    latter reactions are not shown in **Reaction Scheme 12** but specific  
27    examples are described below.

28        5,5-Dimethyl-5,6-dihydro-naphthalen-8(7H)-one-2-carboxylic acid

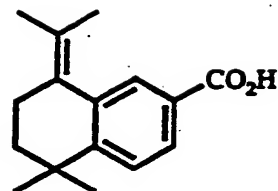
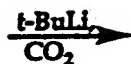
1 (Compound E3) is also coupled with ethyl 4-hydroxybenzoate to provide  
2 ethyl 4-[[[(5,5-dimethyl-8(7H)-one-5,6-dihydronaphthalen-2-  
3 yl)carbonyl]oxy]benzoate (Compound E44) within the scope of Formula

4 2. Compound E44 is subjected to a *Reformatsky* reaction with ethyl  
5 bromoacetate to yield (+/-) ethyl 4-[[[(5,5-dimethyl-8-hydroxy-8-  
6 (carbethoxy)-5,6,7,8-tetrahydronaphthalen-2-yl)carbonyl]oxy]benzoate  
7 (Compound E54). Although the following reactions are not shown in  
8 the scheme, an additional preferred example of compounds of the  
9 invention is obtained when Compound E44 is reduced with sodium  
10 borohydride to give ethyl 4-[[[(5,5-dimethyl-5,6,7,8-tetrahydro-8-hydroxy-  
11 naphthalen-2-yl)carbonyl]oxy]-benzoate (Compound E40). The latter is  
12 converted into tetrahydropyranyl derivatives (within the scope of  
13 Formula 1) as is disclosed in detail in the Specific Examples.

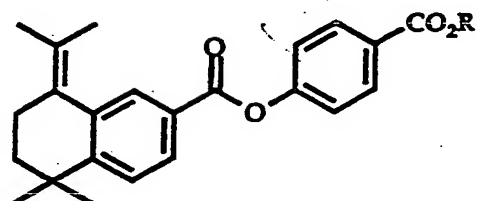
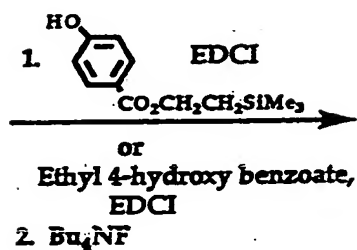
14 To obtain still more specific examples for the compounds of the  
15 invention where the Z group is -COO- or -CONH-  
16 7-bromo-3,4-dihydro-4,4-dimethylnaphthalen-1(2H)-one (Compound G)  
17 is subjected to a *Reformatsky* reaction with ethyl bromoacetate, and the  
18 resulting (+/-) ethyl 2-(1-hydroxy-1,2,3,4-tetrahydro-4,4-dimethyl-7-  
19 bromo-naphthalen-1-yl)acetate (Compound 47) is subjected to the series  
20 of reactions shown in Reaction Scheme 12. These compounds, although  
21 not specifically shown in the scheme, are disclosed in detail in the  
22 appended Specific Examples.



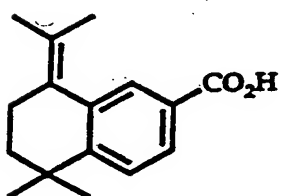
Compound A37



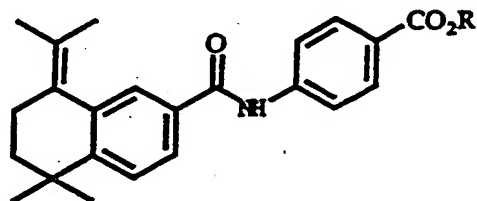
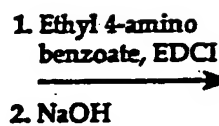
Compound E12



R = CH<sub>2</sub>CH<sub>2</sub>SiMe<sub>3</sub>; Compound E13  
R = H; Compound E14  
R = Et; Compound E15



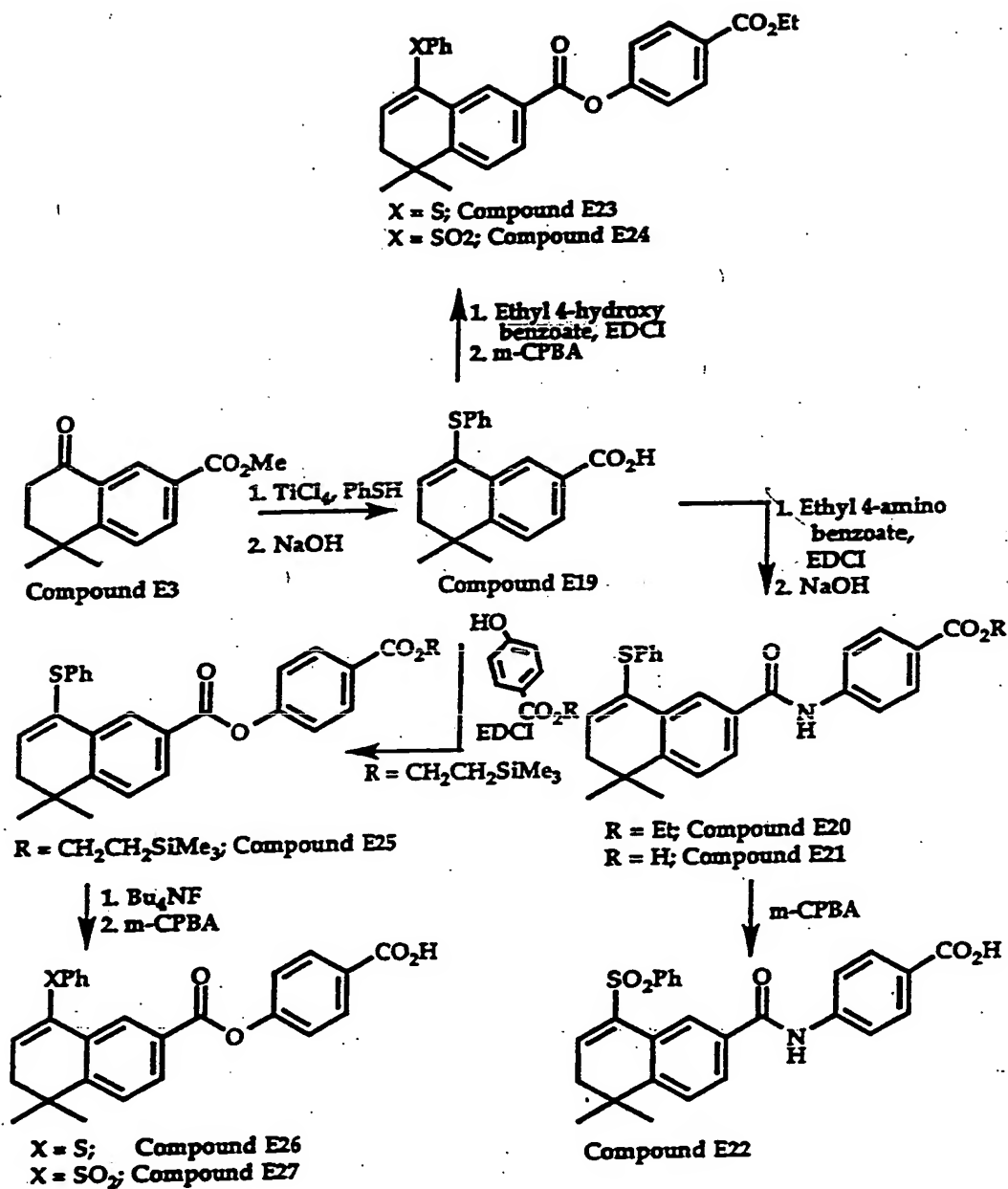
Compound E12



R = Et; Compound E16  
R = H; Compound E17

## Reaction Scheme 13

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Reaction Scheme 14

1        **Reaction Scheme 13** discloses examples for the synthesis of several  
2 preferred compounds of the invention within the scope of **Formula 3**.  
3 The reactions shown in this scheme are analogous to the reactions  
4 disclosed in the foregoing description and reaction schemes and  
5 therefore will be readily understood by those skilled in the art and do  
6 not require further explanation here. A detailed experimental  
7 description for the preparation of compounds shown in this scheme is  
8 provided in the description of the Specific Examples. The same applies  
9 to **Reaction Scheme 14**, which discloses examples for the synthesis of  
10 several preferred compounds of the invention within the scope of  
11 **Formula 5**.

12        Compounds of the invention where with reference to the **Formulas 1**  
13 - 6 the **Z** group is  $\text{-N(O)=N-}$  or  $\text{-N=N(O)-}$  can be prepared by  
14 oxidation of compounds where the **Z** group is  $\text{-N=N-}$ . A suitable  
15 oxidizing agent for this purpose is *meta*-chloroperoxybenzoic acid;  
16 typically both isomers of the azoxy compounds are formed in reactions  
17 using this agent.

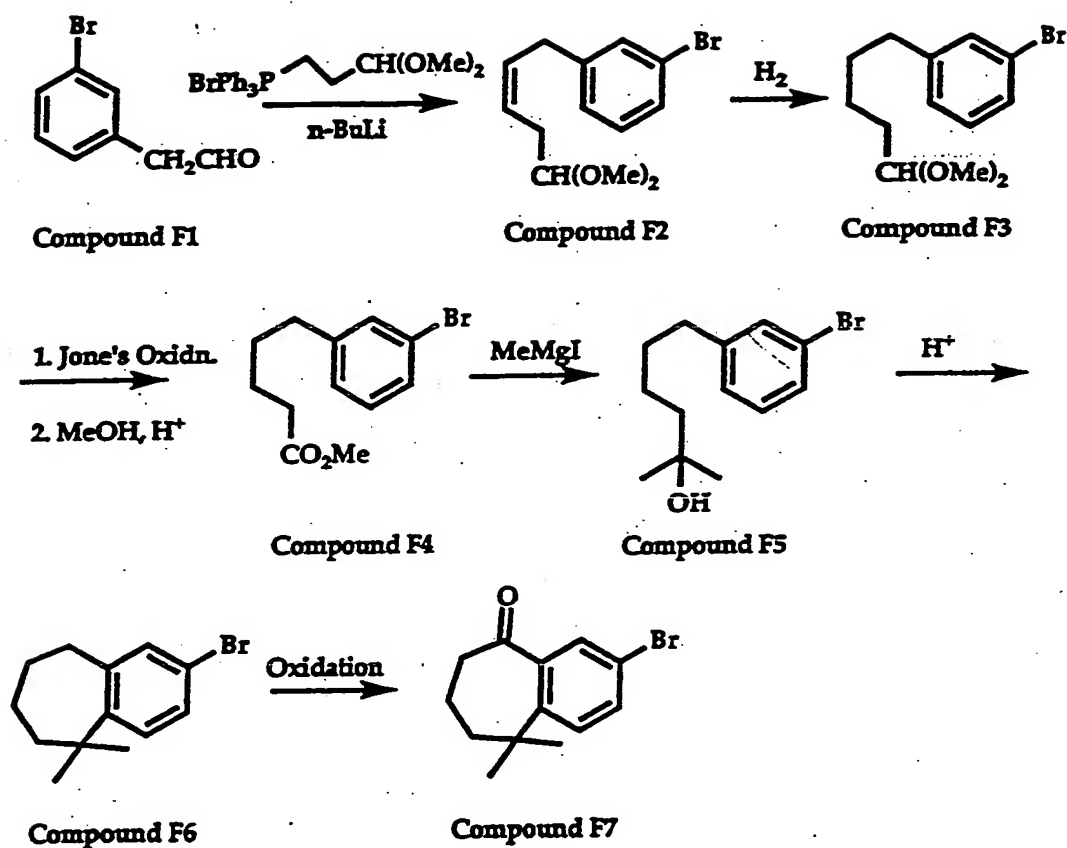
18        Compounds of the present invention where with reference to  
19 **Formula 1 - 6**, **Z** is  $\text{-OCO-}$ ,  $\text{NR}_1\text{CO}$ , as well as the corresponding  
20 thioester and thioamide analogs, can be prepared from the  
21 intermediates having a bromo function on the aromatic portion of the  
22 tetrahydronaphthalene or dihydronaphthalene nucleus, for example such  
23 as **Compounds G, H, A35, A37, B15 and C42**. In these compounds the  
24 bromo function is replaced with an amino or hydroxyl group, in analogy  
25 to the teachings of United States Patent Nos. 5,324,744, the  
26 specification of which is expressly incorporated herein by reference.

27        Compounds of the present invention where with reference to  
28 **Formula 1 - 6**, **Z** is  $\text{-N=CR}_1\text{-}$  or  $\text{-CR}_1\text{=N-}$  will be readily recognized by

1 those skilled in the art as *Schiff* bases. These compounds can be made  
2 by reaction between a primary amine and aldehyde or ketone. In order  
3 to obtain these compounds where the Z is  $-N=CR_1-$  an amine of the  
4 structure where the  $NH_2$  group is attached to the aromatic portion of  
5 the tetrahydronaphthalene or dihydronaphthalene nucleus, is reacted  
6 with an aldehyde or ketone of the structure  $OCR_1-Y(R_2)-A-B$ . An  
7 example for such an amine is Compound D9. *Schiff* bases of the  
8 structure where Z is  $-CR_1=N-$  can be obtained by reaction of an amine  
9 of the formula  $NH_2-Y(R_2)-A-B$  with an aldehyde or ketone where the  
10 aldehyde or ketone function is attached to the aromatic portion of the  
11 tetrahydronaphthalene or dihydronaphthalene nucleus. Compounds  
12 D14a and D14b serve as examples.

13 Compounds of the present invention where with reference to  
14 Formula 1 - 6, the  $X_1$  group is  $[C(R_1)_2]_n$  and n is zero (0), can be made  
15 starting with 6-bromo-indan-1-one (or an appropriately substituted  
16 derivative). In these synthetic schemes 6-bromo-indan-1-one is used in  
17 analogy to 7-bromo-3,4-dihydro-4,4-dimethylnaphthalen-1(2H)-one  
18 (Compound G) as a starting material. 6-bromo-3,3-dimethyl-indan-1-  
19 one is available accordance with the chemical literature. (See Smith,  
20 J.G.,; Massicotte, M.P. Org. Prep. Proced. Int., 1978, 10 123-131.)





Reaction Scheme 15

1 Compounds of the invention where with reference to Formula 1 - 6,  
 2 the  $X_1$  group is  $[C(R_1)_2]_n$  and  $n$  is 2 can be made from 8-bromo-2,3,4,5-  
 3 tetrahydro-5,5-dimethyl-1-(2H)-suberan-one (Compound F7) which is  
 4 used as a starting material in analogy to Compound G. Compound F7  
 5 can be made in accordance with the reaction sequence shown in  
 6 Reaction Scheme 15. As is shown in the scheme, (3-  
 7 bromophenyl)acetaldehyde (Compound F1) is subjected to a *Wittig*  
 8 reaction to obtain a 5 carbon chain attached to the aromatic nucleus,  
 9 and the resulting Compound F2 is hydrogenated and subjected to *Jones*  
 10 oxidation followed by esterification, to provide methyl (3-bromophenyl)-  
 11 pentanoate (Compound F4). Compound F4 is reacted with a Grignard  
 12 reagent to provide a tertiary alcohol (Compound F5), which is cyclized  
 13 to provide 8-bromo-2,3,4,5-tetrahydro-5,5-dimethyl-suberan (Compound  
 14 F6). Compound F6 is oxidized with  $CrO_3$  to yield 8-bromo-2,3,4,5-  
 15 tetrahydro-5,5-dimethyl-1-(2H)-suberan-one (Compound F7).

#### 16 SPECIFIC EXAMPLES

##### 17 Ethyl (4-bromophenyl)acetate (Compound A)

18 A solution of 43 g (200 mmol) of 4-bromophenylacetic acid and 0.2 g  
 19 of conc.  $H_2SO_4$  in 470 ml of ethanol was refluxed for 16 hours. The  
 20 reaction mixture was cooled to ambient temperature, stirred with 6 g of  
 21 solid  $K_2CO_3$  for 30 minutes and then filtered. The filtrate was  
 22 concentrated in vacuo, diluted with  $Et_2O$  (200 ml), washed with 10%  
 23 aqueous  $NaHCO_3$  (10 ml) and brine (10 ml), dried over  $MgSO_4$  and  
 24 concentrated in vacuo to give the title compound as a colorless oil.  
 25 PMR ( $CDCl_3$ ) :  $\delta$  1.25 (3H, t,  $J = 7.0$  Hz), 3.56 (2H, s), 4.15 (2H, q,  $J$   
 26  $= 7.0$  Hz), 7.16 (2H, d,  $J = 8.4$  Hz), 7.45 (2H, d,  $J = 8.4$  Hz).

##### 27 Ethyl (3-bromophenyl)acetate (Compound B)

28 Employing the same general procedure as for the preparation of

1 ethyl (4-bromophenyl)acetate (Compound A), 100 g (463 mmol) of  
2 3-bromophenylacetic acid was converted into the title compound (yellow  
3 oil) using 2 g of conc.  $\text{H}_2\text{SO}_4$  and 500 ml of ethanol.

4 PMR ( $\text{CDCl}_3$ ) :  $\delta$  1.26 (3H, t,  $J = 7.0$  Hz), 3.56 (2H, s), 4.16 (2H, q,  $J$   
5  $= 7.0$  Hz), 7.16-7.26 (2H, m), 7.38-7.46 (2H, m).

6 Ethyl 4-(4-bromophenyl)butanoate (Compound C)

7 To a cold solution ( $-78^\circ\text{C}$ ) of 15 g (62 mmol) of ethyl  
8 (4-bromophenyl)acetate (Compound A) in 150 ml of  $\text{CH}_2\text{Cl}_2$  was added  
9 dropwise (over a span of 1 hour) 65 ml (65 mmol) of  
10 diisobutylaluminum hydride (DIBAL-H, 1M solution in hexane). After  
11 the DIBAL-H addition was complete, the reaction was stirred at  $-78^\circ\text{C}$   
12 for an additional hour. The reaction was quenched by the dropwise  
13 addition of methanol (10 ml), followed by water (10 ml) and 10% HCl  
14 (40 ml). The mixture was then warmed to  $0^\circ\text{C}$ , stirred for 10 minutes  
15 and then washed with water (15 ml), 10% aqueous  $\text{NaHCO}_3$  (10 ml)  
16 and brine (10 ml). The organic phase was dried over  $\text{MgSO}_4$  and the  
17 solvent distilled off at ambient temperature to give crude  
18 (4-bromophenyl)acetaldehyde. To a cold solution ( $0^\circ\text{C}$ ) of this crude  
19 aldehyde in 150 ml of  $\text{CH}_2\text{Cl}_2$  was added a solution of 26 g (74.6 mmol)  
20 of (carbethoxymethylene)triphenylphosphorane in 50 ml of  $\text{CH}_2\text{Cl}_2$ . The  
21 mixture was stirred for 16 hours, concentrated in vacuo and purified by  
22 flash chromatography (silica, 10% EtOAc-hexane) to give ethyl  
23 4-(4-bromophenyl)but-2-enoate as a mixture of E:Z isomers. This  
24 isomeric mixture was dissolved in 150 ml of EtOAc and hydrogenated  
25 over 1 g of 10% Pd/C for 6 hours. The catalyst was filtered off and the  
26 filtrate concentrated in vacuo to give the title compound as a white  
27 solid.

28 PMR ( $\text{CDCl}_3$ ) :  $\delta$  1.26 (3H, t,  $J = 7.1$  Hz), 1.88-1.99 (2H, m), 2.31 (2H,

1 t, J = 7.5 Hz), 2.61 (2H, t, J = 7.5 Hz), 4.28 (2H, q, J = 7.1 Hz), 7.05  
2 (2H, d, J = 8.4 Hz), 7.40 (2H, d, J = 8.4 Hz).

3 Ethyl 4-(3-bromophenyl)butanoate (Compound D)

4 Employing the same general multistep preparation as for ethyl  
5 4-(4-bromophenyl)butanoate (Compound C), 60 g (246 mmol) of ethyl  
6 (3-bromophenyl)acetate (Compound B) was converted into the title  
7 compound (oil) using 255 ml (255 mmol) of diisobutylaluminum hydride  
8 (DIBAL-H, 1M in hexane), 85.8 g (250 mmol) of  
9 (carbethoxymethylene)triphenylphosphorane and 1.7 g of 10% Pd/C.  
10 PMR (CDCl<sub>3</sub>) :  $\delta$  1.26 (3H, t, J = 7.1 Hz), 1.89-2.00 (2H, m), 2.31 (2H,  
11 t, J = 7.5 Hz), 2.63 (2H, t, J = 7.2 Hz), 4.15 (2H, q, J = 7.1 Hz),  
12 7.10-7.35 (4H, m).

13 5-(3-bromophenyl)-2-methylpentan-2-ol (Compound E)

14 To a cold solution (0 °C) of 17 g (63 mmol) of ethyl  
15 4-(3-bromophenyl)butanoate (Compound D) in 40 ml of THF was  
16 added 63 ml (189 mmol) of methylmagnesium bromide (3.0M solution  
17 in THF). The reaction was stirred at 0 °C for 2 hours, quenched by the  
18 slow addition of ice cold water (30 ml) followed by 10% HCl (30 ml)  
19 and then extracted with Et<sub>2</sub>O (4 x 60 ml). The combined organic layer  
20 was washed with 10% aqueous NaHCO<sub>3</sub> (10 ml), water (10 ml) and  
21 brine (10 ml), dried over MgSO<sub>4</sub> and concentrated in vacuo.  
22 Purification by Kugelrohr distillation gave the title compound as a  
23 colorless oil.

24 PMR (CDCl<sub>3</sub>) :  $\delta$  1.20 (6H, s), 1.43-1.55 (2H, m), 1.62-1.78 (2H, m),  
25 2.60 (2H, t, J = 6.0 Hz), 7.10-7.41 (4H, m).

26 6-Bromo-1,2,3,4-tetrahydro-1,1-dimethylnaphthalene (Compound F)

27 15.0 g (58.3 mmol) of 5-(3-bromophenyl)-2-methylpentan-2-ol  
28 (Compound E) was cooled to 0 °C and then 2.8 ml of conc. H<sub>2</sub>SO<sub>4</sub> was

1 added. The mixture was stirred for 2.5 hours, diluted with water (20  
2 ml) and extracted with Et<sub>2</sub>O (3 x 40 ml). The combined organic layers  
3 were washed with water, sat. aqueous NaHCO<sub>3</sub> and brine, dried over  
4 MgSO<sub>4</sub> and concentrated in vacuo. Purification by Kugelrohr  
5 distillation gave the title compound as a colorless oil.

6 PMR (CDCl<sub>3</sub>) :  $\delta$  1.25 (6H, s), 1.61-1.66 (2H, m), 1.74-1.82 (2H, m),  
7 2.73 (2H, t, J = 6.0 Hz), 7.16-7.26 (3H, m).

8 7-Bromo-3,4-dihydro-4,4-dimethylnaphthalen-1(2H)-one (Compound G)

9 To a cold mixture (0 °C) of 209 g (200 mmol) of chromium trioxide,  
10 100 ml (1.06 mol) of acetic anhydride and 200 ml (3.5 mol) of acetic  
11 acid was added a solution of 10 g (41.8 mmol) of 6-bromo-1,2,3,4-tet-  
12 rahydro-1,1-dimethylnaphthalene (Compound F) in 125 ml of benzene.  
13 The reaction mixture was stirred for 1 hour, quenched with ice cold  
14 water and extracted with Et<sub>2</sub>O (3 x 100 ml). The organic layer was dried  
15 over MgSO<sub>4</sub>, concentrated in vacuo, and purified by column  
16 chromatography (silica, 10% EtOAc-hexane) to give the title compound  
17 as a white solid.

18 PMR (CDCl<sub>3</sub>) :  $\delta$  1.28 (6H, s), 2.01 (2H, t, J = 6.0 Hz), 2.72 (2H, t, J =  
19 6.0Hz), 7.31 (1H, d, J = 9.0 Hz), 7.61 (1H, dd, J = 3.0, 9.0 Hz), 8.11  
20 (1H, d, J = 3.0 Hz).

21 6-Bromo-3,4-dihydro-4,4-dimethylnaphthalen-1(2H)-one (Compound H)

22 Employing a published procedure (Mathur, N.C.; Snow, M.S. ;  
23 Young, K. M.; and Pincock, J. A. Tetrahedron, 41, 1509-1516 (1985) ),  
24 ethyl 4-(4-bromophenyl)butanoate (Compound C) was converted into  
25 the title compound. Alternatively, the title compound can be obtained  
26 using similar reactions that were used to convert ethyl  
27 4-(3-bromophenyl)butanoate (Compound D) into  
28 7-bromo-3,4-dihydro-4,4-dimethylnaphthalen-1(2H)-one (Compound G)

1 Ethyl (E)-4-[2-(5,6-dihydro-5,5-dimethyl-naphthalen-8(7H)-one-2-  
 2 yl)ethenyl]-benzoate  
 3 (Compound A2)

4 To a solution of 520.0 mg (2.00 mmol) of 3,4-dihydro-4,4-dimethyl-7-  
 5 bromo-naphthalen-1(2H)-one (Compound G), and 510.0 mg (2.90  
 6 mmol) of ethyl 4-vinylbenzoate in 4.0 mL of triethylamine (degassed by  
 7 sparging with argon for 25 minutes), was added 124.0 mg (0.40 mmol)  
 8 of tris(2-methylphenyl) phosphine, followed by 44.0 mg (0.20 mmol) of  
 9 palladium(II)acetate. The resulting solution was heated to 95 °C for 2.5  
 10 h, cooled to room temperature, and concentrated under reduced  
 11 pressure. Purification by column chromatography (10% EtOAc /  
 12 hexanes) afforded the title compound as a colorless solid.

13 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.41 (t, J = 7.1 Hz, 3H), 1.41 (s, 6H), 2.04 (t, J =  
 14 6.5 Hz, 2H), 2.76 (t, J = 6.5 Hz, 2H), 4.39 (q, J = 7.1 Hz, 2H), 7.20 (s,  
 15 2H), 7.45 (d, J = 8.2 Hz, 1H), 7.57 (d, J = 8.4 Hz, 2H), 7.69 dd, J =  
 16 2.0, 8.2 Hz, 1H), 8.03 (d, J = 8.4 Hz, 2H), 8.19 (d, J = 2.0 Hz, 1H).

17 (E)-4-[2-(5,6,7,8-tetrahydro-5,5-dimethyl-8-oxo-2-naphthalenyl)ethenyl]-  
 18 benzoic acid (Compound A2a)

19 Employing the same general procedure as for the preparation of (E)-4-  
 20 [2-(5,6,7,8-tetrahydro-5,5-dimethyl-8-anti-(O-methyl oxime)-2-  
 21 naphthalenyl)ethenyl]-benzoic acid

22 (Compound A4) 110 mg (0.32 mmol) of ethyl (E)-4-[2-(5,6,7,8-  
 23 tetrahydro-5,5-dimethyl-8-oxo-2-naphthalenyl)ethenyl]-benzoate  
 24 (Compound A2) was converted into the title compound using 1.0 mL  
 25 (1.5 mmol) of LiOH (1.5 M aqueous solution) and 0.5 mL of methanol.  
 26 <sup>1</sup>H NMR (DMSO) δ 1.36 (s, 6 H), 1.96 (t, J = 6.7 Hz, 3 H), 2.69 (t, J  
 27 = 6.7 Hz, 2 H), 7.35 (d, J = 16.4 Hz, 1 H), 7.49 (d, J = 16.4 Hz, 1 H),  
 28 7.58 (d, J = 8.4 Hz, 1 H), 7.74 (d, J = 8.4 Hz, 2 H), 7.89 (overlapping

1 d, 3 H), 8.05 (s, 1 H).

2 Ethyl (E)-4-[2-(5,5-dimethyl-5,6,-dihydro-8(7H)-anti-(O-methyl oxime)-  
3 naphthalen-2-yl)ethenyl]-benzoate (Compound A3)

4 A solution of 298 mg (0.85 mmol) of ethyl (E)-4-[2-(5,5-dimethyl-  
5 5,6,-dihydro-naphthalen-8(7H)-one-2-yl)ethenyl]-benzoate (Compound  
6 A2), 290 mg (3.4 mmol) of methoxylamine hydrochloride and 610 mg  
7 (4.5 mmol) of sodium acetate in 7.0 mL of EtOH and 5.0 mL of  
8 tetrahydrofuran was stirred at ambient temperature for 96 h and  
9 refluxed for 3 h. An additional 0.24 g (1.8 mmol) of methoxylamine  
10 hydrochloride was added and the mixture refluxed for another 1 h. The  
11 mixture was concentrated *in vacuo*, the residue was diluted with water  
12 and extracted with EtOAc (2 x). The combined organic layer was dried  
13 over MgSO<sub>4</sub>, and concentrated *in vacuo*. The crude material was  
14 purified by flash chromatography (silica, 5 % ethyl acetate in hexanes)  
15 to afford the title compound as a yellow oil.

16 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.30 (s, 6 H), 1.41 (t, *J* = 7.1 Hz, 3 H), 1.73 (t, *J*  
17 = 6.9 Hz, 2 H), 2.80 (t, *J* = 6.9 Hz, 2 H), 4.04 (s, 3H), 4.39 (q, *J* = 7.1  
18 Hz, 2 H), 7.13 (d, *J* = 16.4 Hz, 1 H), 7.22 (d, *J* = 16.4 Hz, 1 H), 7.36  
19 (d, *J* = 8.2 Hz, 1 H), 7.50 (dd, *J* = 2.0, 8.2 Hz, 1 H), 7.57 (d, *J* = 8.4  
20 Hz, 2 H), 8.03 (d, *J* = 8.4 Hz, 2 H), 8.11 (d, *J* = 2.0 Hz, 1 H).

21 (E)-4-[2-(5,5-Dimethyl-5,6,-dihydro-8(7H)-anti-(O-methyl oxime)-  
22 naphthalen-2-yl)ethenyl]-benzoic acid (Compound A4)

23 To a solution of 183 mg (0.48 mmol) of ethyl (E)-4-[2-(5,5-dimethyl-  
24 5,6,-dihydro-8(7H)-anti-(O-methyl oxime)-naphthalen-2-yl)ethenyl]-  
25 benzoate (Compound A3) in 4.0 mL of tetrahydrofuran and 1.0 mL of  
26 methanol was added 1.0 mL (2.4 mmol) of LiOH (2.4 M aqueous  
27 solution). The mixture was stirred at ambient temperature for 19 h, and  
28 concentrated *in vacuo*. The residue was diluted with water and acidified

1 to pH 1 with 10% HCl, and extracted with ethyl acetate (2x). The  
 2 organic phase was washed with brine, dried with MgSO<sub>4</sub>, and  
 3 concentrated *in vacuo*. Recrystallization of the crude product using  
 4 acetonitrile afforded the title compound as white crystals.  
 5 <sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 1.24 (s, 6 H), 1.66 (t, *J* = 6.6 Hz, 2 H), 2.72  
 6 (t, *J* = 6.6 Hz, 2 H), 3.95 (s, 1 H), 7.26 (d, *J* = 16.5 Hz, 1 H), 7.44 (d, *J*  
 7 = 8.2 Hz, 1 H), 7.44 (d, *J* = 16.5 Hz, 1 H), 7.67 (d, *J* = 8.2 Hz, 1 H),  
 8 7.74 (d, *J* = 8.1 Hz, 2 H), 7.92 (d, *J* = 8.1 Hz, 2 H), 8.01 (s, 1 H).

9 Ethyl (E)-4-[2-(5,5-dimethyl-5,6,-dihydro-8(7H)-anti-(O-ethyl oxime)-  
 10 naphthalen-2-yl)ethenyl]-benzoate (Compound A5)

11 Employing the same general procedure as for the preparation of  
 12 ethyl (E)-4-[2-(5,5-dimethyl-5,6,-dihydro-8(7H)-anti-(O-methyl oxime)-  
 13 naphthalen-2-yl)ethenyl]-benzoate (Compound A3) 146 mg (0.42 mmol)  
 14 of ethyl (E)-4-[2-(5,5-dimethyl-5,6, dihydronaphthalen-8(7H)-one-2-  
 15 yl)ethenyl]-benzoate (Compound A2) was converted into the title  
 16 compound (white solid) using 167 mg (1.7 mmol) of ethoxylamine  
 17 hydrochloride, 337 mg (2.5 mmol) of sodium acetate, 5.0 mL of EtOH  
 18 and 1.0 mL of tetrahydrofuran.

19 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.28 (s, 6 H), 1.35 (t, *J* = 7.1 Hz, 3 H), 1.39 (t, *J*  
 20 = 7.1 Hz, 3 H), 1.71 (t, *J* = 6.9 Hz, 2 H), 2.80 (t, *J* = 6.9 Hz, 2 H), 4.27  
 21 (q, *J* = 7.1 Hz, 2 H), 4.37 (q, *J* = 7.1 Hz, 2 H), 7.11 (d, *J* = 16.4 Hz, 1  
 22 H), 7.21 (d, *J* = 16.4 Hz, 1 H), 7.34 (d, *J* = 8.2 Hz, 1 H), 7.48 (dd, *J* =  
 23 1.9, 8.2 Hz, 1 H), 7.55 (d, *J* = 8.4 Hz, 2 H), 8.01 (d, *J* = 8.4 Hz, 2 H),  
 24 8.11 (d, *J* = 1.9 Hz, 1 H).

25 (E)-4-[2-(5,5-Dimethyl-5,6,-dihydro-8(7H)-anti-(O-ethyl oxime)-  
 26 naphthalen-2-yl)ethenyl]-benzoic acid (Compound A6)

27 Employing the same general procedure as for the preparation of (E)-  
 28 4-[2-(5,5-dimethyl-5,6,-dihydro--8(7H)-anti-(O-methyl oxime)-



1 naphthalen-2-yl)ethenyl]-benzoic acid (Compound A4) 81 mg (0.21  
 2 mmol) of ethyl (E)-4-[2-(5,5-dimethyl-5,6-dihydro-8(7H)-*anti*-(O-ethyl  
 3 oxime)-naphthalen-2-yl)ethenyl]-benzoate (Compound A5) was  
 4 converted into the title compound (white solid) using 1.0 mL (1.8  
 5 mmol) of LiOH (1.8 M aqueous solution).

6 <sup>1</sup>H NMR (Acetone-D<sub>6</sub>): δ 1.30 (s, 6 H), 1.31 (t, *J* = 7.1 Hz, 3 H), 1.73  
 7 (t, *J* = 6.9 Hz, 2 H), 2.78 (t, *J* = 6.9 Hz, 2 H), 4.23 (q, *J* = 7.1 Hz, 2 H),  
 8 7.30 (d, *J* = 16.4 Hz, 1 H), 7.41 (d, *J* = 16.4 Hz, 1 H), 7.41 (d, *J* = 8.2  
 9 Hz, 1 H), 7.66 (dd, *J* = 1.9, 8.2 Hz, 1 H), 7.76 (d, *J* = 8.4 Hz, 2 H), 8.03  
 10 (d, *J* = 8.4 Hz, 2 H), 8.15 (d, *J* = 1.9 Hz, 1 H).

11 Ethyl (E)-4-[2-(5,5-dimethyl-5,6,-dihydro-8(7H)-*anti*-(oxime))-  
 12 naphthalen-2-yl)ethenyl]-benzoate (Compound A7)

13 Employing the same general procedure as for the preparation of  
 14 ethyl (E)-4-[2-(5,5-dimethyl-5,6,-dihydro-8(7H)-*anti*-(O-methyl oxime)-  
 15 naphthalen-2-yl)ethenyl]-benzoate (Compound A3) 190 mg (0.55 mmol)  
 16 of ethyl (E)-4-[2-(5,5-dimethyl-5,6-dihydronaphthalen-8(7H)-one-2-  
 17 yl)ethenyl]-benzoate (Compound A2) was converted into the title  
 18 compound using 152 mg (1.7 mmol) of hydroxylamine hydrochloride,  
 19 430 mg (3.2 mmol) of sodium acetate, 6.0 mL of EtOH and 1.0 mL of  
 20 tetrahydrofuran.

21 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.32 (s, 6 H), 1.41 (t, *J* = 7.1 Hz, 3 H), 1.77 (t, *J*  
 22 = 7.0 Hz, 2 H), 2.91 (t, *J* = 7.0 Hz, 2 H), 4.39 (q, *J* = 7.1 Hz, 2 H),  
 23 7.13 (d, *J* = 16.4 Hz, 1 H), 7.20 (d, *J* = 16.4 Hz, 1 H), 7.39 (d, *J* = 8.2  
 24 Hz, 1 H), 7.49 (m, *J* = 1.8 Hz, 1 H), 7.53 (d, *J* = 8.4 Hz, 2 H), 8.02 (d,  
 25 *J* = 8.4 Hz, 2 H), 8.08 (d, *J* = 1.8 Hz, 1 H), 8.48 (s, 1 H).

26 (E)-4-[2-(5,5-Dimethyl-5,6,-dihydronaphthalen-8(7H)-*anti*(oxime)-2-  
 27 yl)ethenyl]-benzoic acid (Compound A8)

28 Employing the same general procedure as for the preparation of (E)-

1 4-[2-(5,5-dimethyl-5,6,-dihydro-8(7H)-*anti*-(O-methyl oxime)-naphthalen-  
 2 2-yl)ethenyl]-benzoic acid (Compound A4) 104 mg (0.29 mmol) of ethyl  
 3 (E)-4-[2-(5,5-dimethyl-5,6,-dihydro-8(7H)-*anti*-(oxime)-naphthalen-2-  
 4 yl)ethenyl]-benzoate (Compound A7) was converted into the title  
 5 compound using 1.0 mL (1.5 mmol) of LiOH (1.5 M aqueous solution).  
 6 <sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 1.24 (s, 6 H), 1.66 (t, *J* = 6.7 Hz, 2 H), 1.71  
 7 (t, *J* = 6.7 Hz, 2 H), 7.23 (d, *J* = 16.5 Hz, 1 H), 7.41 (d, *J* = 8.3 Hz, 1  
 8 H), 7.42 (d, *J* = 16.5 Hz, 1 H), 7.62 (dd, *J* = 1.7, 8.3 Hz, 1 H), 7.73 (d, *J*  
 9 = 8.5 Hz, 2 H), 7.92 (d, *J* = 8.5 Hz, 2 H), 8.03 (d, *J* = 1.7 Hz, 1 H).

10 Ethyl (E)-4-[2-(5,6-dihydro-5,5-dimethyl-8-(trifluoromethylsulfonyl)oxy-  
 11 naphthalen-2-yl)ethenyl]-benzoate (Compound A9)

12 To a cold (-78 °C) solution of 440.0 mg (2.40 mmol) of sodium  
 13 bis(trimethylsilyl)amide in 10.0 mL of THF was added 700.0 mg (2.00  
 14 mmol) of ethyl (E)-4-[2-(5,6-dihydro-5,5-dimethyl-naphthalen-8(7H)-  
 15 one-2-yl)ethenyl]-benzoate (Compound A2) as a solution in 25.0 mL of  
 16 THF. After stirring at -78°C for 1.5 h, 960.0 mg (2.40 mmol) of 2[*N,N*-  
 17 bis trifloromethylsulfonyl)amino]-5-chloropyridine was added in one  
 18 portion. After 30 min, the solution was warmed to 0°C and stirred for 3  
 19 h. The reaction was quenched by the addition of saturated aqueous  
 20 NH<sub>4</sub>Cl, and extracted with EtOAc. The combined extracts were washed  
 21 with 5% aqueous NaOH, dried (NaSO<sub>4</sub>), and the solvents removed  
 22 under reduced pressure. The title compound was isolated as a colorless  
 23 solid after column chromatography (7% EtOAc / hexanes).  
 24 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.32 (s, 6H), 1.41 (t, *J* = 7.1 Hz, 3H), 2.43 (d, *J* =  
 25 4.9 Hz, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 6.00 (t, *J* = 4.9 Hz, 1H), 7.10 (d,  
 26 *J* = 16.4 Hz, 1H), 7.20 (d, *J* = 16.4 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H),  
 27 7.49 (d, *J* = 8.0 Hz, 1H), 7.52 (s, 1H), 7.57 (d, *J* = 8.4 Hz, 2H), 8.04 (d,  
 28 *J* = 8.4 Hz, 1H).

1 Ethyl (E)-4-[2-(5,5-dimethyl-8-(thiazol-2-yl)-5,6-dihydronaphthalen-2-  
 2 yl)ethenyl]-benzoate (Compound A10)

3 To a cold (-78 °C) solution of thiazole (0.38 g (0.10 mL, 1.4 mmol)  
 4 in THF (2.0 mL) was added n-butyl lithium (1.6 M solution in hexanes,  
 5 0.5 mL, 0.8 mmol) and stirred for 30 min. To this solution was added  
 6 0.176 g (1.3 mmol) of zinc chloride in 3.0 mL of tetrahydrofuran and  
 7 stirred for 45 min. The resulting turbid solution was transferred, via  
 8 cannula, to a flask containing a mixture of 0.17 g (0.35 mmol) of ethyl  
 9 (E)-4-[2-(5,5-dimethyl-8-(trifluoromethylsulfonyl)oxy-5,6-  
 10 dihydronaphthalen-2-yl)ethenyl] benzoate (Compound A9) and 15 mg  
 11 (0.01 mmol) of tetrakis(triphenylphosphine)palladium(0) in 3.0 mL of  
 12 tetrahydrofuran. The reaction mixture was stirred for 1 h at ambient  
 13 temperature and 1.5 h at 55 °C. The reaction mixture was treated with  
 14 aqueous NH<sub>4</sub>Cl, and extracted with EtOAc (2 x). The combined  
 15 organic layer was washed with brine and dried (MgSO<sub>4</sub>). The solvent  
 16 was removed under reduced pressure and the crude product was  
 17 purified by flash chromatography (silica, 20% ethyl acetate in hexane) to  
 18 afford the title compound as a white solid.

19 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.34 (s, 6 H), 1.40 (t, *J* = 7.1 Hz, 3 H), 2.41 (d, *J*  
 20 = 4.9 Hz, 2 H), 4.37 (q, *J* = 7.1 Hz, 2 H), 6.56 (t, *J* = 4.9 Hz, 1 H),  
 21 7.03 (d, *J* = 16.4 Hz, 1 H), 7.18 (d, *J* = 16.4 Hz, 1 H), 7.34 (d, *J* = 3.4  
 22 Hz, 1 H), 7.38 (d, *J* = 8.1 Hz, 1 H), 7.48 (dd, *J* = 1.8, 8.4 Hz, 1 H),  
 23 7.53 (d, *J* = 8.4 Hz, 2 H), 7.86 (d, *J* = 1.8 Hz, 1 H), 7.93 (d, *J* = 3.4 Hz,  
 24 1 H), 8.00 (d, *J* = 8.4 Hz, 2 H).

25 (E)-4-[2-(5,5-Dimethyl-8-(thiazol-2-yl)-5,6-dihydronaphthalen-2-  
 26 yl)ethenyl]-benzoic acid (Compound A12)

27 Employing the same general procedure as for the preparation of (E)-4-  
 28 [2-(5,5-dimethyl-5,6-dihydro-8(7H)-*anti*-(O-methyl oxime)-naphthalen-2-

1 yl)ethenyl]-benzoic acid (Compound A4), 20 mg (0.05 mmol) of ethyl  
 2 (E)-4-[2-(5,6-dihydro-5,5-dimethyl-8-(thiazol-2-yl)-naphthalen-2-  
 3 yl)ethenyl]-benzoate (Compound A10) was converted into the title  
 4 compound (white solid).

5  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.28 (s, 6 H), 2.39 (d,  $J = 4.9$  Hz, 2 H), 6.63 (t,  $J$   
 6 = 4.9 Hz, 1 H), 7.15 (d,  $J = 16.4$  Hz, 1 H), 7.36 (d,  $J = 16.4$  Hz, 1 H),  
 7 7.43 (d,  $J = 8.2$  Hz, 1 H), 7.63 (d,  $J = 8.2$  Hz, 1 H), 7.70 (d,  $J = 8.2$   
 8 Hz, 2 H), 7.77 (d,  $J = 3.3$  Hz, 1 H), 7.90 (m,  $J = 8.2$  Hz, 3 H), 7.97 (d,  
 9  $J = 3.3$  Hz, 1 H).

10 Ethyl (E)-4-[2-(5,5-dimethyl-8-(2-thienyl)-5,6-dihydronaphthalen-2-  
 11 yl)ethenyl]-benzoate (Compound A13)

12 A solution of lithiothiophene was prepared by the addition of 0.10 g  
 13 (0.095 mL, 1.2 mmol) of thiophene to a cold solution ( $-78^\circ\text{C}$ ) of 0.61 g  
 14 (0.90 mL, 1.4 mmol, 1.6 M in hexanes) of *n*-butyl lithium in 2.0 mL of  
 15 tetrahydrofuran. The solution was stirred at  $-78^\circ\text{C}$  for 35 min and then  
 16 a solution of 0.158 g (1.2 mmol) of zinc chloride in 2.0 mL of  
 17 tetrahydrofuran was added. The resulting solution was stirred at  $-78^\circ\text{C}$   
 18 to room temperature for 1 h and then the organozinc was added via  
 19 cannula to a mixture of 0.212 g (0.44 mmol) of ethyl (E)-4-[2-(5,5-  
 20 dimethyl-8-(trifluoromethylsulfonyl)oxy-5,6-dihydronaphthalen-2-  
 21 yl)ethenyl] benzoate (Compound A9) and 18 mg (0.016 mmol) of  
 22 tetrakis(triphenylphosphine)palladium(0) in 2.0 mL of tetrahydrofuran.  
 23 The resulting mixture was stirred at room temperature for 10 min and  
 24 then heated at  $50^\circ\text{C}$  for 1 h. The reaction was quenched by the  
 25 addition of sat. aqueous  $\text{NH}_4\text{Cl}$ . The mixture was extracted with  
 26 EtOAc (2x), and washed with brine. The organic phase was dried over  
 27  $\text{Na}_2\text{SO}_4$  and then concentrated *in vacuo*. The crude material product  
 28 was purified by flash chromatography (silica, 15 % ethyl acetate in

1 hexanes) to afford the title compound as a solid.

2 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.34 (s, 6 H), 1.40 (t, *J* = 7.1 Hz, 3 H), 2.34 (d, *J*  
3 = 4.8 Hz, 2 H), 4.37 (q, *J* = 7.1 Hz, 2 H), 6.22 (t, *J* = 4.8 Hz, 1 H),  
4 7.02 (d, *J* = 16.4 Hz, 1 H), 7.10- 7.12 (m, 2 H), 7.15 (d, *J* = 16.4 Hz, 1  
5 H), 7.29-7.33 (m, 1 H), 7.37 (d, *J* = 8.0 Hz, 1 H), 7.45 (dd, *J* = 1.8, 8.0  
6 Hz, 1 H), 7.52 (d, *J* = 8.5 Hz, 2 H), 7.53 (d, *J* = 1.8 Hz, 1 H), 8.00 (d,  
7 *J* = 8.4 Hz, 2 H).

8 (E)-4-[2-(-5,5-Dimethyl-8-(2-thienyl)-5,6-dihydronaphthalen-2-  
9 yl)ethenyl]-benzoic acid (Compound A15)

10 Employing the same general procedure as for the preparation of (E)-4-  
11 [2-(5,5-dimethyl-5,6,-dihydro-8(7H)-*anti*-(O-methyl oxime)-naphthalen-2-  
12 yl)ethenyl]-benzoic acid (Compound A4) 98 mg (0.24 mmol) of ethyl  
13 (E)-4-[2-(-5,5-dimethyl-8-(2-thienyl)-5,6-dihydronaphthalen-2-yl)ethenyl]-  
14 benzoate (Compound A13) was converted into the title compound  
15 (white solid).

16 <sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 1.27 (s, 6H), 2.32 (d, *J* = 4.8 Hz, 2 H), 6.23  
17 (t, *J* = 4.8 Hz, 1 H), 7.14 (d, *J* = 16.4 Hz, 1 H), 7.14- 7.15 (overlapping  
18 d, 2 H), 7.36 (d, *J* = 16.4 Hz, 1 H), 7.43 (d, *J* = 8.1 Hz, 1 H), 7.48 (d, *J*  
19 = 1.7 Hz, 1 H), 7.54 (t, *J* = 3.1 Hz, 1 H), 7.62 (dd, *J* = 1.7, 8.1 Hz, 1  
20 H), 7.68 (d, *J* = 8.4 Hz, 2 H), 7.88 (d, *J* = 8.4 Hz, 2 H).

21 Ethyl (E)-4-[2-(5,6-dihydro-5,5-dimethyl-8-(phenylthio)-  
22 naphthalenyl)ethenyl] benzoate (Compound A16)

23 To a degassed solution of 0.35 g (1.0 mmol) of 2-bromo-5,6-dihydro-  
24 5,5-dimethyl-8-(phenylthio)-naphthalene (Compound A35) and 0.34 g  
25 (1.9 mmol) of ethyl 4-vinylbenzoate in 4.0 mL of triethylamine, was  
26 added 0.066 g (0.2 mmol) of tri-*o*-tolylphosphine and then 0.025 g (0.1  
27 mmol) of palladium(II) acetate. The reaction was heated at 90 °C for  
28 2.25 h. The reaction was concentrated *in vacuo*. The residue was

1 purified by flash chromatography (silica, 5 % ethyl acetate in hexane),  
 2 followed by recrystallization using EtOH to afford the title compound as  
 3 white crystals.

4  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.35 (s, 6 H), 1.40 (t,  $J = 7.1$  Hz, 3 H), 2.41 (d,  $J$   
 5 = 4.7 Hz, 2 H), 4.38 (q,  $J = 7.1$  Hz, 2 H), 6.55 (t,  $J = 4.7$  Hz, 1 H),  
 6 6.93 (d,  $J = 16.3$  Hz, 1 H), 7.08-7.16 (m, 2 H), 7.22-7.27 (m, 6 H), 7.32  
 7 (d,  $J = 8.2$  Hz, 1 H), 7.38 (dd,  $J = 1.7, 8.0$  Hz, 1 H), 7.49 (d,  $J = 8.4$   
 8 Hz, 2 H), 7.81 (d,  $J = 1.7$  Hz, 1 H), 8.00 (d,  $J = 8.4$  Hz, 2 H).

9 Ethyl (E)-4-[2-(5,6-dihydro-5,5-dimethyl-8-(phenylsulfonyl)-  
 10 naphthalenyl)ethenyl] benzoate (Compound A17)

11 To a solution of 0.090 g (0.2 mmol) of ethyl (E)-4-[2-(5,6-dihydro-  
 12 5,5-dimethyl-8-(phenylthio)-naphthalenyl)ethenyl] benzoate (Compound  
 13 A16) in 2.0 mL of methylene chloride was added dropwise a solution of  
 14 140 mg (0.45 mmol, 50-60 %) of m-chloroperoxybenzoic acid in 2.0 mL  
 15 of methylene chloride and the reaction stirred at room temperature for  
 16 3.5 h. The mixture was diluted with water and extracted with methylene  
 17 chloride (2x). The organic phase was dried over  $\text{MgSO}_4$  and  
 18 concentrated *in vacuo*. The crude product was purified by flash  
 19 chromatography (silica, 30 % ethyl acetate in hexanes) followed by  
 20 recrystallization in EtOH to afford the title compound as a solid.

21  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.22 (s, 6 H), 1.42 (t,  $J = 7.1$  Hz, 3 H), 2.50 (d,  $J$   
 22 = 4.9 Hz, 2 H), 4.39 (q,  $J = 7.1$  Hz, 2 H), 7.00 (d,  $J = 16.4$  Hz, 1 H),  
 23 7.13 (d,  $J = 16.4$  Hz, 1 H), 7.29 (d,  $J = 8.4$  Hz, 1 H), 7.40 (dd,  $J = 1.7,$   
 24 8.1 Hz, 1 H), 7.46-7.57 (m, 6 H), 7.97 (m, 2 H), 8.04 (d,  $J = 8.4$  Hz, 2  
 25 H), 8.11 (d,  $J = 1.7$  Hz, 1 H).

26 (E)-4-[2-(5,6-dihydro-5,5-dimethyl-8-(phenylthio)-naphthalen-2-  
 27 yl)ethenyl] benzoic acid (Compound A18)

28 Employing the same general procedure as for the preparation of

1 (E)-4-[2-(5,5-dimethyl-5,6-dihydro-8(7H)-*anti*-(O-methyl oxime)-  
 2 naphthalen-2-yl)ethenyl]-benzoic acid (Compound A4), 60 mg (0.14  
 3 mmol) of ethyl (E)-4-[2-(5,6-dihydro-5,5-dimethyl-8-(phenylthio)-  
 4 naphthalen-2-yl)ethenyl] benzoate (Compound A16) was converted into  
 5 the title compound (white solid).

6 <sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 1.29 (s, 6 H), 2.40 (d, *J* = 4.6 Hz, 3 H), 6.61  
 7 (t, *J* = 4.6 Hz, 1 H), 7.05 (d, *J* = 16.4 Hz, 1 H), 7.17-7.20 (m, 1 H),  
 8 7.28-7.35 (m, 4 H), 7.38 (d, *J* = 8.1 Hz, 1 H), 7.52 (dd, *J* = 1.6, 8.1 Hz,  
 9 1 H), 7.67 (d, *J* = 8.4 Hz, 2 H), 7.73 (d, *J* = 1.6 Hz, 1 H), 7.90 (d, *J* =  
 10 8.4 Hz, 2 H).

11 (E)-4-[2-(5,6-dihydro-5,5-dimethyl-8-(phenylsulfonyl)-  
 12 naphthalenyl)ethenyl] benzoic acid (Compound A19)

13 To a cold solution (0 °C) of 61 mg (0.15 mmol) of (E)-4-[2-(5,6-  
 14 dihydro-5,5-dimethyl-8-(phenylthio)-naphthalen-2-yl)ethenyl] benzoic  
 15 acid (Compound A18) in 5.0 mL of methylene chloride and 2.0 mL of  
 16 tetrahydrofuran was added dropwise a cold solution (0 °C) of 70 mg  
 17 (0.22 mmol, 50-60%) of *m*-chloroperoxybenzoic acid in 4.0 mL of  
 18 methylene chloride and the reaction stirred at 0 °C for 7 min. The  
 19 mixture was diluted with water and extracted with methylene chloride  
 20 (2x). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in*  
 21 *vacuo*. Recrystallization from acetonitrile gave the title compound as a  
 22 solid.

23 <sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 1.16 (s, 6 H), 2.54 (d, *J* = 4.6 Hz, 2 H), 7.08  
 24 (d, *J* = 16.4 Hz, 1 H), 7.35-7.41 (m, 2 H), 7.48 (t, *J* = 4.6 Hz, 1 H), 7.56  
 25 (d, *J* = 8.7 Hz, 1 H), 7.63-7.68 (m, 3 H), 7.75 (d, *J* = 8.2 Hz, 2 H),  
 26 7.93-7.96 (m, 3 H), 8.03 (d, *J* = 8.2 Hz, 2 H).

27 Ethyl (E)-4-[2-(5,6-dihydro-5,5-dimethyl-8-(ethylthio)-naphthalen-2-  
 28 yl)ethenyl] benzoate (Compound A20)

To a degassed solution of 0.50 g (1.7 mmol) of 2-bromo-5,6-dihydro-5,5-dimethyl-8-(ethylthio)-naphthalene (Compound A36) and 0.45 g (2.5 mmol) of ethyl 4-vinylbenzoate in 4.0 mL of triethylamine, was added 109 mg (0.36 mmol) of tri-*o*-tolylphosphine and then 35 mg (0.16 mmol) of palladium(II) acetate. The reaction was heated at 90 °C for 2.25 h. The reaction was concentrated *in vacuo* and purified by flash chromatography (silica, 2 % ethyl acetate in hexane) to afford the title compound as a colorless oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.29 (s, 6 H), 1.30 (t, *J* = 7.4 Hz, 3 H), 1.41 (t, *J* = 7.1 Hz, 3 H), 2.31 (d, *J* = 4.8 Hz, 2 H), 2.75 (q, *J* = 7.4 Hz, 2 H), 4.38 (q, *J* = 7.1 Hz, 2 H), 6.20 (t, *J* = 4.8 Hz, 1 H), 7.12 (d, *J* = 16.3 Hz, 1 H), 7.24 (d, *J* = 16.3 Hz, 1 H), 7.32 (d, *J* = 8.0 Hz, 1 H), 7.41 (dd, *J* = 1.7, 8.0 Hz, 1 H), 7.57 (d, *J* = 8.4 Hz, 2 H), 7.89 (d, *J* = 1.7 Hz, 1 H), 8.02 (d, *J* = 8.4 Hz, 2 H).

(E)-4-[-2-(5,6-dihydro-5,5-dimethyl-8-(ethylthio)-naphthalen-2-yl)ethenyl] benzoic acid (Compound A21)

Employing the same general procedure as for the preparation of (E)-4-[2-(5,5-dimethyl-5,6-dihydro-8(7H)-*anti*-(O-methyl oxime)-naphthalen-2-yl)ethenyl]-benzoic acid (Compound A4), 206 mg (0.52 mmol) of ethyl (E)-4-[-2-(5,6-dihydro-5,5-dimethyl-8-(ethylthio)-naphthalen-2-yl)ethenyl] benzoate (Compound A20) was converted into the title compound (white solid).

<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 1.22 (t, *J* = 7.1 Hz, 3 H), 1.23 (s, 6 H), 2.27 (d, *J* = 4.9 Hz, 2 H), 2.75 (q, *J* = 7.1 Hz, 2 H), 6.15 (t, *J* = 4.9 Hz, 1 H), 7.24 (d, *J* = 16.4 Hz, 1 H), 7.37 (d, *J* = 8.1 Hz, 1 H), 7.45 (d, *J* = 16.4 Hz, 1 H), 7.75 (m, 3 H), 7.92 (d, *J* = 8.1 Hz, 2 H).

(E)-4-[-2-(5,6-dihydro-5,5-dimethyl-8-(ethylsulfonyl)-naphthalen-2-yl)ethenyl] benzoate (Compound A22)



To a cold solution (0 °C) of 44 mg (0.12 mmol) of ethyl (E)-4-[2-(5,6-dihydro-5,5-dimethyl-8-(ethylthio)-naphthalen-2-yl)ethenyl] benzoic acid (Compound A21) in 4.0 mL of methylene chloride and 0.5 mL of tetrahydrofuran was added dropwise a cold solution (0 °C) of 55 mg (0.18 mmol, 50-60%) of m-chloroperoxybenzoic acid in 3.0 mL of methylene chloride and the reaction stirred at 0 °C for 30 min. The mixture was diluted with water and extracted with methylene chloride (2x). The organic phase was diluted with EtOAc, dried over Na<sub>2</sub>SO<sub>4</sub> and then concentrated *in vacuo*. Recrystallization from acetonitrile gave the title compound as a solid.

<sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 1.16 (t, *J* = 7.3 Hz, 1 H), 1.25 (s, 6 H), 2.50 (d, *J* = 4.8 Hz, 2 H), 3.32 (q, *J* = 7.3 Hz, 2 H), 7.18 (t, *J* = 4.8 Hz, 1 H), 7.25 (d, *J* = 16.4 Hz, 1 H), 7.46 (d, *J* = 16.4 Hz, 1 H), 7.49 (d, *J* = 8.1 Hz, 1 H), 7.71 (dd, *J* = 1.5, 8.1 Hz, 1 H), 7.76 (d, *J* = 8.4 Hz, 2 H), 7.94 (d, *J* = 8.4 Hz, 2 H), 8.04 (d, *J* = 1.5 Hz, 1 H).

Ethyl (E)-4-[2-(5,6,7,8-tetrahydro-5,5-dimethyl-8-(1,3-dithian-2-yl)naphthalen-2-yl)ethenyl] benzoate (Compound A23)

To a cold solution (0 °C) of 140 mg (0.40 mmol) of ethyl (E)-4-[2-(5,5-dimethyl-5,6,-dihydro-naphthalen-8(7H)-one-2-yl)ethenyl]-benzoate (Compound A2), in 6.0 mL of methylene chloride was added dropwise 130 mg (0.12 mL, 1.2 mmol) of 1,3-propanedithiol and 0.17g (0.15 mL, 102 mmol) of borontrifluoride diethyl etherate. The reaction stirred between 0 °C and room temperature for 4 h. The mixture was diluted with aqueous sat. potassium carbonate, and extracted with ether (2x). The organic phase was washed with brine, dried over MgSO<sub>4</sub> and then concentrated *in vacuo*. The crude product was purified by flash chromatography (silica, 10 % ethyl acetate in hexane) to afford the title compound as a solid.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.29 (s, 6 H), 1.39 (t, *J* = 7.1 Hz, 3 H), 1.83 (m, 2 H), 2.00 (m, 1 H), 2.09 (m, 1 H), 2.62 (m, 2 H), 2.74 (m, 2 H), 3.17 (m, 2 H), 4.36 (q, *J* = 7.1 Hz, 2 H), 7.09 (d, *J* = 16.4 Hz, 1 H), 7.20 (d, *J* = 16.4 Hz, 1 H), 7.30 (d, *J* = 8.2 Hz, 1 H), 7.41 (dd, *J* = 1.9, 8.2 Hz, 1 H), 7.55 (d, *J* = 8.4 Hz, 2 H), 8.00 (d, *J* = 8.4 Hz, 1 H), 8.10 (d, *J* = 1.9 Hz, 2 H).

(E)-4-[2-(5,6,7,8-Tetrahydro-5,5-dimethyl-8-(2-(1,3-dithian-2-yl)naphthalenyl)ethenyl]-benzoic acid (Compound A24)

Employing the same general procedure as for the preparation of (E)-4-[2-(5,5-dimethyl-5,6,-dihydro-8(7H)-*anti*-(O-methyl oxime)-naphthalen-2-yl)ethenyl]-benzoic acid (Compound A4), 81 mg (0.18 mmol) of ethyl (E)-4-[2-(5,6,7,8-tetrahydro-5,5-dimethyl-8-(1,3-dithian-2-yl)naphthalen-2-yl)ethenyl] benzoate (Compound A23) was converted into the title compound (white solid).

<sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 1.28 (s, 6 H), 1.83 (m, 2 H), 1.93 (m, 1 H), 2.19 (m, 1 H), 2.66 (m, 4 H), 3.22 (m, 2 H), 7.18 (d, *J* = 16.4 Hz, 1 H), 7.28 (d, *J* = 16.4 Hz, 1 H), 7.36 (d, *J* = 8.2 Hz, 1 H), 7.48 (dd, *J* = 1.9, 8.2 Hz, 1 H), 7.66 (d, *J* = 8.4 Hz, 2 H), 8.00 (d, *J* = 8.4 Hz, 1 H), 8.12 (d, *J* = 1.9 Hz, 2 H).

Ethyl (E)-4-[2-(5,6-tetrahydro-5,5-dimethyl-8-(propyliden-2-yl)-naphthalen-2-yl)ethenyl]-benzoate (Compound A25)

To a degassed solution of 0.36 g (1.3 mmol) of 7-bromo-1(2H)-(propyliden-2-yl)-3,4-dihydro-4,4-dimethylnaphthalene (Compound A37) and 0.44 g (2.5 mmol) of ethyl 4-vinylbenzoate in 3.6 g (5.0 mL, 36 mmol) of triethylamine, was added 88 mg (0.29 mmol) of tri-*o*-tolylphosphine and then 33 mg (0.15 mmol) of palladium(II) acetate. The reaction was heated at 95 °C for 4 h. The reaction was concentrated *in vacuo* and purified by flash chromatography (silica, 1%

1 ethyl acetate in hexane) to afford the title compound as an oil.

2  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.24 (s, 6 H), 1.39 (t,  $J = 7.1$  Hz, 3 H), 1.64 (t,  $J$   
3  $= 6.8$  Hz, 2 H), 1.89 (s, 3 H), 2.00 (s, 3 H), 2.51 (t,  $J = 6.8$  Hz, 2 H),  
4 4.38 (q,  $J = 7.1$  Hz, 2 H), 7.02 (d,  $J = 16.4$  Hz, 1 H), 7.18-7.37  
5 (overlapping d, 3 H), 7.41 (s, 1 H), 7.58 (d,  $J = 8.4$  Hz, 2 H), 8.02 (d,  $J$   
6  $= 8.4$  Hz, 2 H).

7 (E)-4-[2-(5,6-dihydro-5,5-dimethyl-8(7H)-(propyliden-2-yl)-naphthalen-2-  
8 yl)ethenyl]-benzoic acid (Compound A26)

9 Employing the same general procedure as for the preparation of (E)-4-  
10 [2-(5,5-dimethyl-5,6,-dihydro-8(7H)-*anti*-(O-methyl oxime)-naphthalen-2-  
11 yl)ethenyl]benzoic acid (Compound A4) 95 mg (0.25 mmol) of ethyl  
12 (E)-4-[2-(5,6,7,8-tetrahydro-5,5-dimethyl-8-(methylethyliden-2-  
13 yl)naphthalen-2-yl)ethenyl]benzoate (Compound A25) was converted  
14 into the title compound using 1.0 mL (2.3 mmol) of LiOH (2.3 M  
15 aqueous solution).

16  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.26 (s, 6 H), 1.64 (t,  $J = 6.9$  Hz, 2 H), 1.86 (s, 3  
17 H), 2.02 (s, 3 H), 2.53 (t,  $J = 6.9$  Hz, 2 H), 7.07 (d,  $J = 16.4$  Hz, 1 H),  
18 7.22-7.38 (overlapping d, 3 H), 7.42 (s, 1 H), 7.58 (d,  $J = 8.4$  Hz, 2 H),  
19 8.08 (d,  $J = 8.4$  Hz, 2 H).

20 Ethyl (E)-4-[2-(7,8-dihydro-5,5-dimethyl-8(7H)-(pentyliden-3-yl)-  
21 naphthalen-2-yl)ethenyl]-benzoate (Compound A27)

22 To a degassed solution of 0.30 g (0.98 mmol) of 7-bromo-1(2H)-  
23 (pentyliden-3-yl)3,4-dihydro-4,4-dimethylnaphthalene (Compound A38)  
24 and 0.17 g (0.97 mmol) of ethyl 4-vinylbenzoate in 3.63 g (5.0 mL, 36  
25 mmol) of triethylamine, was added 61 mg (0.2 mmol) of tri-o-  
26 tolylphosphine and then 23 mg (0.10 mmol) of palladium(II) acetate.  
27 The reaction was heated at 95 °C for 6.5 h. The reaction was then  
28 concentrated *in vacuo* and purified by flash chromatography (silica, 100

1 % hexane) followed by recrystallization from ethanol gave the title  
2 compound as white crystals.

3  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.05 (t,  $J = 7.3$  Hz, 3 H), 1.20 (t,  $J = 7.4$  Hz, 3  
4 H), 1.24 (s, 6 H), 1.39 (t,  $J = 7.2$  Hz, 3 H), 1.65 (t,  $J = 6.8$  Hz, 2 H),  
5 2.22 (q,  $J = 7.4$  Hz, 2 H), 2.31 (q,  $J = 7.3$  Hz, 2 H), 2.50 (t,  $J = 6.8$   
6 Hz, 2 H), 4.36 (q,  $J = 7.2$  Hz, 2 H), 7.04 (d,  $J = 16.4$  Hz, 1 H), 7.17 (d,  
7  $J = 16.4$  Hz, 1 H), 7.28 (d,  $J = 8.1$  Hz, 1 H), 7.34 (d,  $J = 8.1$  Hz, 1 H),  
8 7.39 (s, 1 H), 7.53 (d,  $J = 8.4$  Hz, 2 H), 8.00 (d,  $J = 8.4$  Hz, 2 H).

9 (E)-4-[2-(5,6-Dihydro-5,5-dimethyl-8(7H)-(pentyliden-3-yl)-naphthalen-2-  
10 yl)ethenyl]benzoic acid (Compound A28)

11 Employing the same general procedure as for the preparation of (E)-  
12 4-[2-(5,5-dimethyl-5,6,-dihydro-8(7H)-*anti*-(O-methyl oxime)-naphthalen-  
13 2-yl)ethenyl]-benzoic acid (Compound A4), 150 mg (0.37 mmol) of ethyl  
14 (E)-4-[2-(5,6,-dihydro-5,5-dimethyl-8(7H)-(pentyliden-3-yl)-naphthalen-2-  
15 yl)ethenyl]-benzoate (Compound A27) was converted into the title  
16 compound (white solid).

17  $^1\text{H}$  NMR (Acetone- $\text{D}_6$ ):  $\delta$  1.08 (t,  $J = 7.4$  Hz, 3 H), 1.22 (t,  $J = 7.1$  Hz,  
18 3 H), 1.26 (s, 6 H), 1.67 (t,  $J = 7.1$  Hz, 3 H), 2.25 (q,  $J = 7.4$  Hz, 2 H),  
19 2.33 (q,  $J = 7.4$  Hz, 2 H), 2.50 (t,  $J = 7.1$  Hz, 2 H), 7.13 (d,  $J = 16.4$   
20 Hz, 1 H), 7.28 (d,  $J = 16.4$  Hz, 1 H), 7.31 (d,  $J = 8.6$  Hz, 1 H), 7.34 (m,  
21 2 H), 7.62 (d,  $J = 8.4$  Hz, 2 H), 7.98 (d,  $J = 8.4$  Hz, 2 H).

22 Ethyl (E)-4-[2-(5,6-dihydro-5,5-dimethyl-8(7H)-  
23 (cyclohexylidenyl)naphthalen-2-yl)ethenyl]-benzoate (Compound A29)

24 To a degassed solution of 0.40 g (1.3 mmol) of 7-bromo-1(2H)-  
25 (cyclohexylidenyl)-3,4-dihydro-4,4-dimethylnaphthalene (Compound A39)  
26 and 0.62 g (3.5 mmol) of ethyl 4-vinylbenzoate in 2.2 g (3.0 mL, 22  
27 mmol) of triethylamine, was added 76 mg (0.25 mmol) of tri-*o*-  
28 tolylphosphine and then 29 mg (0.13 mmol) of palladium(II) acetate.

1 The reaction was heated at 95 °C for 2.5 h. The reaction was then  
 2 concentrated *in vacuo* and purified by flash chromatography (silica, 1 %  
 3 ethyl acetate in hexane) to afford the title compound as a white solid.  
 4 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.27 (s, 6 H), 1.39 (t, *J* = 7.1 Hz, 3 H), 1.62 (m, 8  
 5 H), 2.34 (m, 2 H), 2.53 (m, 4 H), 4.37 (q, *J* = 7.1 Hz, 2 H), 7.04 (d, *J*  
 6 = 16.4 Hz, 1 H), 7.18 (d, *J* = 16.4 Hz, 1 H), 7.28-7.35 (m, 3H), 7.53 (d,  
 7 *J* = 8.4 Hz, 2 H), 8.01 (d, *J* = 8.4 Hz, 2 H).

8 (E)-4-[2-(5,6-Dihydro-5,5-dimethyl-8(7H)-(cyclohexylidenyl)-naphthalen-  
 9 2-yl)ethenyl]benzoic acid (Compound A31)

10 Employing the same general procedure as for the preparation of (E)-4-  
 11 [2-(5,5-dimethyl-5,6,-dihydro-8(7H)-*anti*-(O-methyl oxime)-naphthalen-2-  
 12 yl)ethenyl]-benzoic acid (Compound A4), 280 mg (0.68 mmol) of ethyl  
 13 (E)-4-[2-(5,6-dihydro-5,5-dimethyl-8(7H)-(cyclohexylidenyl)-naphthalen-  
 14 2-yl)ethenyl]benzoate (Compound A29) was converted into the title  
 15 compound using 2.0 mL (3.3 mmol) of LiOH (1.7 M aqueous solution).  
 16 <sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 1.28 (s, 6 H), 1.59-1.67 (m, 8 H), 2.36 (m, 2  
 17 H), 2.48-2.57 (m, 4 H), 7.08 (d, *J* = 16.3 Hz, 1 H), 7.20-7.38 (m, 5 H),  
 18 7.59 (d, *J* = 8.4 Hz, 1 H), 8.09 (d, *J* = 8.4 Hz, 2 H).

19 (+/-) Ethyl (E)-4-[2-(5,6,7,8-tetrahydro-5,5-dimethyl-8-hydroxy-8-  
 20 (methylcarbethoxy)naphthalen-2-yl)ethenyl] benzoate (Compound A32)

21 To a refluxing solution of 0.75 g ( 11.5 mmol) of granular zinc in 5.0  
 22 mL of benzene was added a solution of ethyl (E)-4-[2-(5,5-dimethyl-  
 23 5,6,-dihydro-naphthalen-8(7H)-one-2-yl)ethenyl]-benzoate (Compound  
 24 A2) in 5.0 mL of benzene followed by 0.27 g (0.18 mmol) of ethyl  
 25 bromoacetate. The resulting mixture was refluxed for 24 h. The  
 26 reaction was cooled, filtered through celite. The filtrate was washed  
 27 with 10% HCl, sat. aqueous NaHCO<sub>3</sub> and brine. The organic phase  
 28 was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The crude material

1 was purified by flash chromatography (silica, 10 % ethyl acetate in  
2 hexane) to afford the title compound as a white solid.

3  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.30 (t,  $J = 7.1$  Hz, 3 H), 1.30 (3H, s), 1.34 (3H,  
4 s), 1.41 (t,  $J = 7.1$  Hz, 3 H), 1.77 (m, 2 H), 2.09 (m, 2 H), 2.82 (d,  $J =$   
5 3.4 Hz, 2 H), 4.17 (s, 1 H), 4.22 (q,  $J = 7.1$  Hz, 2 H), 4.38 (q,  $J = 7.1$   
6 Hz, 2 H), 7.10 (d,  $J = 16.4$  Hz, 1 H), 7.20 (d,  $J = 16.4$  Hz, 1 H), 7.31  
7 (d,  $J = 8.2$  Hz, 1 H), 7.42 (dd,  $J = 1.9, 8.2$  Hz, 1 H), 7.55 (d,  $J = 8.4$   
8 Hz, 2 H), 7.75 (d,  $J = 1.9$  Hz, 1 H), 8.03 (d,  $J = 8.4$  Hz, 2 H).

9 Ethyl (E)-4-[2-(5,6-dihydro-5,5-dimethyl-8-  
10 (methylcarbethoxy)naphthalen-2-yl)ethenyl]benzoate (Compound A33a)  
11 Ethyl (E)-4-[2-(5,6-dihydro-5,5-dimethyl-8(7H)-anti  
12 (carbethoxymethylidenyl)-naphthalen-2-yl)ethenyl]benzoate (Compound  
13 A33b)

14 To a solution of 0.25 g (0.57 mmol) of (+/-)ethyl (E)-4-[2-(5,6,7,8-  
15 tetrahydro-5,5-dimethyl-8-hydroxy-8-(methylcarbethoxy)-naphthalen-2-  
16 yl)ethenyl] benzoate (Compound A32) in 11.0 mL of benzene was  
17 added 1.0 g (4.2 mmol) of *Burgess* reagent and the resulting solution  
18 was heated at 55°C for 30 min. The reaction was cooled and  
19 concentrated *in vacuo*, the residue was diluted with water and extracted  
20 with EtOAc (2 x), the organic layers were washed with brine, dried over  
21  $\text{Na}_2\text{SO}_4$ , and concentrated *in vacuo* to afford a mixture of title  
22 compounds in a 3:1 ratio (endo: exo). The title compounds were  
23 separated by flash chromatography (silica, 5 % ethyl acetate in hexane)  
24 to afford the pure isomers as white solids.

25 **Compound A33a:**

26  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.21 (t,  $J = 7.1$  Hz, 3 H), 1.30 (s, 6H), 1.41 (t,  $J =$   
27 7.1 Hz, 3 H), 2.82 (d,  $J = 4.3$  Hz, 2 H), 3.51 (s, 2 H), 4.12 (q,  $J = 7.1$   
28 Hz, 2 H), 4.38 (q,  $J = 7.1$  Hz, 2 H), 5.97 (t,  $J = 4.3$  Hz, 1 H), 7.05

1 (d,  $J = 16.4$  Hz, 1 H), 7.19 (d,  $J = 16.4$  Hz, 1 H), 7.30-7.40 (m, 3 H),  
 2 7.47 (d,  $J = 8.4$  Hz, 2 H), 8.03 (d,  $J = 8.4$  Hz, 2 H).

3 4,4-Dimethyl-7-bromo-1-phenylthio-3,4-dihydronaphthalene (Compound  
 4 A35)

5 To a stirred solution of 4,4-dimethyl-7-bromo-3,4-dihydronaphthalen-  
 6 1(2H)one (Compound G, 1.48 g, 5.9 mmol), titanium tetrachloride (1.09  
 7 g, 5.7 mmol) and THF (10 mL) was added a mixture of thiophenol  
 8 (660 mg, 6 mmol), triethylamine (1.16 g, 11.5 mmol) and THF (20 mL)  
 9 via an addition funnel at ambient temperature. The mixture was stirred  
 10 for 5 h, and water (10 mL) was added, extracted with ether (3 X 50  
 11 mL). The combined organic layer was washed successively with water  
 12 (10 mL), 10%  $\text{NaHCO}_3$  (10 mL) and brine (10 mL). The organic layer  
 13 was dried ( $\text{MgSO}_4$ ) and the solvent distilled off at reduced pressure.  
 14 After silicagel chromatography the title compound was obtained as a  
 15 colorless oil .

16  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) :  $\delta$  1.31 (s, 6H), 2.39 (d,  $J = 4.9$  Hz, 2H), 6.54 (t,  $J$   
 17 = 4.9 Hz, 1H), 7.10-7.35 (m, 7H), 7.78 (d,  $J = 2.0$  Hz, 1H).

18 2-Bromo-5,6-dihydro-5,5-dimethyl-8-(ethylthio)-naphthalene  
 19 (Compound A36)

20 To a solution of 1.03 g (4.1 mmol) of 7-bromo-3,4-dihydro-4,4-  
 21 dimethylnaphthalen-1(2H)-one (Compound G) in 30.0 mL of  
 22 tetrahydrofuran, was added dropwise 0.49 g (0.85 mL, 7.8 mmol) of  
 23 titaniumtetrachloride and the resulting solution stirred for 10 min. A  
 24 solution of 35 mg (0.50 mL, 6.7 mmol) of ethanethiol and 0.54 g (0.75  
 25 mL, 5.4 mmol) of triethylamine in 10.0 mL of tetrahydrofuran was  
 26 added and the reaction stirred at room temperature for 13 h. The  
 27 mixture was diluted with water and extracted with ether (2x). The  
 28 organic phase was washed with brine, dried over  $\text{Na}_2\text{SO}_4$  and then

1 concentrated *in vacuo*. Purification by flash chromatography (silica, 100  
2 % hexane) gave the title compound as an oil.

3  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.25 (s, 6 H), 1.27 (t,  $J = 7.1$  Hz, 3 H), 2.29 (d,  $J$   
4 = 4.8 Hz, 2 H), 2.70 (q,  $J = 7.1$  Hz, 2 H), 6.23 (t,  $J = 4.8$  Hz, 1 H),  
5 7.17 (d,  $J = 8.2$  Hz, 1 H), 7.35 (dd,  $J = 1.7, 8.2$  Hz, 1 H), 7.85 (d,  $J =$   
6 2.1 Hz, 2 H).

7 7-Bromo-1(2H)-(propyliden-2-yl)-3,4-dihydro-4,4-dimethylnaphthalene  
8 (Compound A37)

9 To a slurry of titanium trichloride (5 g, 32 mmol) in DME (80 mL)  
10 was added lithium wire in small portions (0.7 g, 100 mmol) under argon  
11 atmosphere. The mixture was refluxed for 1 h, cooled to ambient  
12 temperature and a solution of acetone (928 mg, 16 mmol) and 7-bromo-  
13 3,4-dihydro-4,4-dimethylnaphthalen-1(2H)-one (Compound G, 1.0 g,  
14 3.96 mmol) in 20 mL of DME was added. The resultant mixture was  
15 refluxed for 16 h under argon atmosphere. The reaction mixture was  
16 then cooled to ambient temperature and diluted with hexane (100 mL),  
17 And thereafter filtered through a pad of florisil. The filtrate was  
18 concentrated under reduced pressure and purified by flash  
19 chromatography (silica, 100% hexane) to afford the title compound as a  
20 colorless oil.

21  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.19 (s, 6H), 1.56 (t,  $J = 6.9\text{Hz}$ , 2H), 1.81 (s, 3H),  
22 1.94 (s, 3H), 2.44 (t,  $J = 7.1\text{Hz}$ , 2H), 7.11 (d,  $J = 8.3\text{Hz}$ , 1H), 7.23 (dd,  
23  $J = 2.1, 8.4\text{Hz}$ , 1H), 7.35 (d,  $J = 2.1\text{Hz}$ , 1H).

24 7-Bromo-1(2H)-(pentyliden-2-yl)-3,4-dihydro-4,4-dimethylnaphthalene  
25 (Compound A38)

26 Employing the same general procedure as for the preparation  
27 of 7-bromo-1(2H)-(propyliden-2-yl)-3,4-dihydro-4,4-  
28 dimethylnaphthalene (Compound A37), 1.0 g (3.97 mmol) of 4,4-



1 dimethyl-7-bromo-3,4-dihydronaphthalen-1(2H)one (Compound G)  
 2 was converted into the title compound using 1.37 g (15.9 mmol) of  
 3 3-pentanone, 1.92 g (277 mmol) of lithium and 12.2 g (79.4 mmol)  
 4 of titanium trichloride.

5  $^1\text{H}$ NMR ( $\text{CDCl}_3$ ):  $\delta$  1.04 (t,  $J$  = 7.5 Hz, 3H), 1.14 (t,  $J$  = 7.5 Hz,  
 6 3H), 1.23 (s, 6H), 1.63 (t,  $J$  = 7.1 Hz, 2H), 2.21 (q,  $J$  = 7.5 Hz,  
 7 2H), 2.29 (q,  $J$  = 7.5 Hz, 2H), 2.49 (t,  $J$  = 7.1 Hz, 2H), 7.15 (d,  $J$   
 8 = 8.3 Hz, 1H), 7.29 (dd,  $J$  = 2.2, 8.3 Hz, 1H), 7.36 (d,  $J$  = 2.2  
 9 Hz, 1H).

10 7-Bromo-1(2H)-(cyclohexylidenyl)-3,4-dihydro-4,4-  
 11 dimethylnaphthalene (Compound A39)

12 Employing the same general procedure as for the preparation  
 13 of 7-bromo-1(2H)-(propyliden-2-yl)-3,4-dihydro-4,4-  
 14 dimethylnaphthalene (Compound A37), 1.0 g (3.97 mmol) of 4,4-  
 15 dimethyl-7-bromo-3,4-dihydronaphthalen-1(2H)one (Compound G)  
 16 was converted into the title compound using 1.56 g (15.9 mmol) of  
 17 cyclohexanone, 1.92 g (277 mmol) of lithium and 12.2 g (79.4  
 18 mmol) of titanium trichloride.

19  $^1\text{H}$ MNR ( $\text{CDCl}_3$ ):  $\delta$  1.23 (s, 6H), 1.50-1.65 (m, 8H), 2.33 (br s,  
 20 2H), 2.45 (t,  $J$  = 5.5 Hz, 2H), 2.50 (t,  $J$  = 7.1 Hz, 2H), 7.15 (d,  $J$   
 21 = 8.1 Hz, 1H), 7.26 (d,  $J$  = 1.6 Hz, 1H), 7.29 (br s, 1H).

22 Ethyl-6-[5,6,7,8-tetrahydro-5,5-dimethyl-naphth-7-yl]naphth-2-oate  
 23 (Compound B1)

24 To a degassed solution of 0.39 g (1.4 mmol) of ethyl 6-bromo-  
 25 naphthalene-2-carboxylate and 3.0 mL of toluene, was added  
 26 sequentially 49 mg (0.04 mmol) of tetrakis-triphenylphosphine  
 27 palladium(0), 2.0 mL (2.0 mmol) of 1M sodium carbonate and  
 28 then a solution of 0.32 g (1.6 mmol) of (5,6,7,8-tetrahydro-5,5-

1 dimethylnaphth-2-yl)boronic acid (Compound B13) in 3.0 mL of  
 2 MeOH. The reaction was heated at 80 °C for 6 h, diluted with 2N  
 3 Na<sub>2</sub>CO<sub>3</sub>, and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x), the organic layer was  
 4 washed with brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo*  
 5 to give an oil. Flash chromatography (silica, 5 % ethyl acetate in  
 6 hexane) of the crude material gave the title compound as a white  
 7 solid.

8 <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 1.35 (s, 6 H), 1.46 (t, J = 7.1  
 9 Hz, 3 H), 1.70-1.74 (m, 2 H), 1.85-1.89 (m, 2 H), 2.88 (t, J = 6.3  
 10 Hz, 2 H), 4.46 (q, J = 7.1 Hz, 2H), 7.42 (d, J = 1.7 Hz, 1 H),  
 11 7.46 (d, J = 8.2 Hz, 1 H), 7.52 (dd, J = 2.0, 8.2 Hz, 1 H), 7.80  
 12 (dd, J = 1.7, 8.5 Hz, 1 H), 7.91 (d, J = 8.6 Hz, 1 H), 8.00 (d, J =  
 13 8.5 Hz, 1 H), 8.05 (s, 1 H), 8.08 (dd, J = 1.7, 8.6 Hz, 1 H), 8.61  
 14 (s, 1 H).

15 6-[5,6,7,8-Tetrahydro-5,5-dimethyl-naphth-7-yl]-2-naphthoic acid  
 16 (Compound B2)

17 Employing the same general procedure as for the preparation of  
 18 (E)-4-[2-(5,6,7,8-tetrahydro-5,5-dimethyl-8-anti-(O-methyl oxime)-  
 19 naphthalen-2-yl)ethenyl]-benzoic acid (Compound A4) 50 mg (0.14  
 20 mmol) of ethyl-6-[5,6,7,8-tetrahydro-5,5-dimethyl-naphth-7-  
 21 yl]naphth-2-oate (Compound B1) was converted into the title  
 22 compound (white solid).

23 <sup>1</sup>H NMR (DMSO-D<sub>6</sub>, 300 MHz): δ 1.28 (s, 6 H), 1.64-1.68 (m, 2  
 24 H), 1.77-1.80 (m, 2 H), 2.82 (t, J = 5.7 Hz, 2 H), 7.48 (d, J = 8.4  
 25 Hz, 1 H), 7.49 (s, 1 H), 7.58 (d, J = 8.4 Hz, 1 H), 7.89 (dd J = 1.8,  
 26 8.7 Hz, 1 H), 7.98 (dd, J = 1.8, 8.7 Hz, 1 H), 8.05 (d, J = 8.7 Hz, 1  
 27 H), 8.17 (d, J = 8.7 Hz, 1 H), 8.24 (s, 1 H), 8.60 (s, 1 H).

28 Ethyl-6-[5,6,7,8-tetrahydro-5,5-dimethyl-8-(t-butyl dimethylsilyloxy)-

1 naphth-7-yl]naphth-2-oate (Compound B3)

2 To a degassed solution of 722 mg (2.6 mmol) of ethyl 6-bromo-  
 3 naphthalenecarboxylate in 6.0 mL of toluene, was added  
 4 sequentially 90 mg (0.08 mmol) of tetrakis-triphenylphosphine  
 5 palladium (0), 5.0 mL (10.0 mmol) of 2M sodium carbonate, and a  
 6 solution of 1.018 g (3.1 mmol) of (5,6,7,8-tetrahydro-5,5-dimethyl-  
 7 8-(t-butyldimethylsilyloxy)naphth-2-yl)boronic acid (Compound  
 8 B14) in 3.0 mL of MeOH. The reaction was heated at 90 °C for  
 9 15 h. The reaction was diluted with 2N Na<sub>2</sub>CO<sub>3</sub>, and extracted  
 10 with CH<sub>2</sub>Cl<sub>2</sub> (2 x), the organic layer was washed with brine, dried  
 11 over MgSO<sub>4</sub>, and concentrated *in vacuo* to give an oil. The  
 12 crude product was purified flash chromatography (silica, 5 % ethyl  
 13 acetate in hexane) to afford the title compound as a white solid.  
 14 <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 0.20 (s, 3 H), 0.23 (s, 3 H), 1.00 (s,  
 15 9 H), 1.35 (s, 6 H), 1.46 (t, 3 H, *J* = 7.1 Hz), 1.70-2.10 (m, 4 H), 4.46  
 16 (q, *J* = 7.1 Hz, 2H), 4.83 (dd, *J* = 4.7, 8.2 Hz, 1 H), 7.42 (d, *J* =  
 17 8.2 Hz, 1 H), 7.60 (dd, *J* = 2.1, 8.2 Hz, 1 H), 7.79-7.82 (overlapping  
 18 s, dd, 2 H), 7.90 (d, *J* = 8.7 Hz, 1 H), 7.92 (d, *J* = 8.5 Hz, 1 H),  
 19 8.06-8.1 (overlapping s, dd, 2 H), 8.62 (s, 1 H).

20 Ethyl-6-[5,6,7,8-tetrahydro-5,5-dimethyl-8-hydroxy-naphth-7-  
 21 yl]naphth-2-oate (Compound B4)

22 To a cold (0 °C) solution of 1.15 g (2.4 mmol) of ethyl-6-  
 23 [5,6,7,8-tetrahydro-5,5-dimethyl-8-(t-butyldimethylsilyloxy)-naphth-  
 24 7-yl]naphth-2-oate  
 25 (Compound B3) in 12.0 mL of tetrahydrofuran, was added 3.1 g  
 26 (12.0 mL, 12.0 mmol, 1.0 M in tetrahydrofuran) of  
 27 tetrabutylammoniumfluoride and the mixture was stirred between  
 28 0 °C to room temperature for 3 h. The reaction was then

1 concentrated *in vacuo*, diluted with water, and extracted with ether  
 2 (2 x), the organic layer was washed with brine, dried over MgSO<sub>4</sub>,  
 3 and concentrated *in vacuo* to give a solid. Recrystallization from  
 4 ethanol gave the title compound as a white solid.

5 <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 1.32 (s, 3 H), 1.39 (s, 3 H), 1.46 (t, J = 7.1 Hz, 3 H), 1.66-1.72 (m, 1 H), 1.90-1.99 (m, 3 H), 2.11-2.20 (m, 1 H), 4.47 (q, J = 7.1 Hz, 2H), 4.85 (t, J = 5.0 Hz, 1H), 7.46 (d, J = 8.2 Hz, 1 H), 7.63 (dd, J = 2.1, 8.2 Hz, 1 H), 7.81 (dd, J = 1.8, 8.7 Hz, 1 H), 7.83 (s, 1 H), 7.90 (d, J = 8.5 Hz, 1 H), 8.00 (d, J = 8.7 Hz, 1 H), 8.08 (overlapping, 2 H), 8.61 (s, 1 H).

11 6-[5,6,7,8-Tetrahydro-5,5-dimethyl-8-hydroxy-naphth-7-yl]-2-  
 12 naphthoic acid  
 13 (Compound B5)

14 Employing the same general procedure as for the preparation  
 15 of (E)-4-[2-(5,6,7,8-tetrahydro-5,5-dimethyl-8-*anti*-(O-methyl  
 16 oxime)-naphthalen-2-yl)ethenyl]-benzoic acid (Compound A4) 124  
 17 mg (0.33 mmol) of ethyl-6-[5,6,7,8-tetrahydro-5,5-dimethyl-8-  
 18 hydroxy-naphth-7-yl]naphth-2-oate (Compound B4) was converted  
 19 into the title compound.

20 <sup>1</sup>H NMR (DMSO, 300 MHz): δ 1.25 (s, 3 H), 1.29 (s, 3 H), 1.58-  
 21 1.99 (m, 4 H), 3.33 (s, 1 H), 4.62 (s, 1 H), 7.47 (d, J = 8.2 Hz, 1  
 22 H), 7.66 (dd, J = 2.0, 8.2 Hz, 1 H), 7.85 (d, J = 2.0 Hz, 1 H), 7.89  
 23 (dd J = 1.7, 8.6 Hz, 1 H), 8.00 (dd, J = 1.7, 8.6 Hz, 1 H), 8.07 (d,  
 24 J = 8.6 Hz, 1 H), 8.19 (d, J = 8.6 Hz, 1 H), 8.24 (s, 1 H), 8.61 (s,  
 25 1 H).

26 Ethyl -6-[5,5-dimethyl-5,6-dihydro--naphthlen-8(7H)-one-2-yl]-  
 27 naphthalen-2-oate (Compound B6)

28 To a solution of 101 mg (0.27 mmol) of ethyl-6-[5,6,7,8-

1 tetrahydro-5,5-dimethyl-8-hydroxy-naphth-7-yl]naphth-2-oate  
 2 (Compound B4) in 1.5 mL of methylene chloride was added 50  
 3 mg (0.43 mmol) of N-methylmorpholine N-oxide and 6.0 mg  
 4 (0.017 mmol) of tetrapropylammonium perruthenate(VII). The  
 5 reaction was stirred at room temperature for 3 h, diluted with  
 6 water, and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x). The combined organic  
 7 layer was washed with brine, dried over MgSO<sub>4</sub>, and concentrated  
 8 *in vacuo* to give a foam. The title compound was obtained as a  
 9 white solid after flash chromatography (silica, 10% ethyl acetate in  
 10 hexane).

11 <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 1.46 (overlapping s, 6 H), 1.46  
 12 (overlapping t, *J* = 7.1 Hz, 3 H), 2.09 (t, *J* = 6.4 Hz, 2 H), 2.80  
 13 (t, *J* = 6.4 Hz, 2 H), 4.46 (q, *J* = 7.1 Hz, 2H), 7.57 (d, *J* = 8.2  
 14 Hz, 1 H), 7.83 (dd, *J* = 1.8, 8.6 Hz, 1 H), 7.90-7.95 (several d, 2  
 15 H), 8.04 (d, *J* = 8.4 Hz, 1 H), 8.09-8.12 (overlapping s, dd, 2 H),  
 16 8.41 (d, *J* = 2.1 Hz, 1 H), 8.63 (s, 1 H).

17 6-[5,5-Dimethyl-5,6-dihydro--naphthlen-8(7H)-one-2-yl]-2-  
 18 naphthoic acid (Compound B7)

19 Employing the same general procedure as for the preparation  
 20 of (E)-4-[2-(5,6,7,8-tetrahydro-5,5-dimethyl-8-anti-(O-methyl  
 21 oxime)-2-naphthalenyl)ethenyl]-benzoic acid (Compound A4) 58  
 22 mg (0.16 mmol) of ethyl -6-[5,5-dimethyl-5,6-dihydro--naphthlen-  
 23 8(7H)-one-2-yl]-naphthalen-2-oate (Compound B6) was converted  
 24 into the title compound (white solid).

25 <sup>1</sup>H NMR (DMSO-D<sub>6</sub>, 300 MHz): δ 1.41 (s, 6 H), 2.01 (t, *J* =  
 26 6.7 Hz, 2 H), 2.74 (t, *J* = 6.7 Hz, 2 H), 7.71 (d, *J* = 8.3 Hz, 1  
 27 H), 7.93 (dd, *J* = 1.8, 8.7 Hz, 1 H), 7.93 (dd, *J* = 1.7, 8.5 Hz, 1  
 28 H), 8.07-8.13 (several d, 3 H), 8.22 (d, *J* = 8.5 Hz, 1 H), 8.26 (s, 2

1 H), 8.32 (s, 1 H), 8.63 (s, 1 H).

2 Ethyl-6-[5,6,7,8-tetrahydro-5,5-dimethyl-8-(methoxymethoxy)-  
3 naphth-7-yl]naphth-2-oate (Compound B8)

4 To a cold (0 °C) solution of 130 mg (0.35 mmol) of ethyl-6-  
5 [5,6,7,8-tetrahydro-5,5-dimethyl-8-(hydroxy)-naphth-7-yl]naphth-2-  
6 oate (Compound B4) in 2.0 mL of methylene chloride was added  
7 50 mg (0.15 mL, 0.86 mmol) of Hunig's base, followed by 0.21 g  
8 (0.20 mL, 2.6 mmol) chloromethyl methyl ether was added and  
9 stirred at room temperature for 14 h. About 500 mgs of t-  
10 butylammonium iodide was then added and the reaction was  
11 warmed to 35 °C for one additional hour. The reaction was  
12 diluted with water, and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x). The  
13 combined organic layer was washed with brine, dried over  
14 MgSO<sub>4</sub>, and concentrated *in vacuo* to give an oil. The title  
15 compound was obtained as an oil after flash chromatography  
16 (silica, 10 % ethyl acetate).

17 <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 1.31 (s, 3 H), 1.40 (s, 3 H), 1.46  
18 (t, 3 H, *J* = 7.1 Hz), 1.60 (m, 1 H), 1.98-2.08 (m, 3 H), 3.51 (s, 3  
19 H), 4.46 (q, *J* = 7.1 Hz, 2H), 4.75 (t, *J* = 4.5 Hz, 1 H), 4.83 (d, *J*  
20 = 7.0 Hz, 1 H), 4.93 (d, *J* = 7.0 Hz, 1 H), 7.48 (d, *J* = 8.2 Hz,  
21 1 H), 7.63 (dd, *J* = 2.0, 8.2 Hz, 1 H), 7.70 (d, *J* = 2.0 Hz, 1 H),  
22 7.80 (dd *J* = 1.7, 8.5 Hz, 1 H), 7.92 (d, *J* = 8.5 Hz, 1 H), 8.01 (d, *J*  
23 = 8.7 Hz, 1 H), 8.05 (s, 1 H), 8.09 (dd, *J* = 1.7, 8.7 Hz, 1 H),  
24 8.62 (s, 1 H).

25 6-[5,6,7,8-Tetrahydro-5,5-dimethyl-8-(methoxymethoxy)-naphth-7-  
26 yl]-2-naphthoic acid (Compound B9)

27 Employing the same general procedure as for the preparation  
28 of (E)-4-[2-(5,6,7,8-tetrahydro-5,5-dimethyl-8-anti-(O-methyl

1 oxime)-2-naphthalenyl]ethenyl]-benzoic acid (Compound A4) 90  
 2 mg (0.21 mmol) of ethyl-6-[5,6,7,8-tetrahydro-5,5-dimethyl-8-  
 3 (methoxymethoxy)-naphth-7-yl]naphth-2-oate (Compound B8)  
 4 was converted into the title compound (white solid).

5 <sup>1</sup>H NMR (DMSO-D<sub>6</sub>, 300 MHz): δ\_1.26 (s, 3 H), 1.34 (s, 3 H),  
 6 1.59 (m, 1 H), 1.98 (m, 3 H), 3.34 (s, 3 H), 4.68 (t, *J* = 4.5 Hz, 1  
 7 H), 4.78 (d, *J* = 6.8 Hz, 1 H), 4.84 (d, *J* = 6.8 Hz, 1 H), 7.54 (d,  
 8 *J* = 8.3 Hz, 1 H), 7.70 (s, 1 H), 7.73 (d, *J* = 8.3 Hz, 1 H), 7.90 (d,  
 9 *J* = 8.7 Hz, 1 H), 8.00 (d, *J* = 8.7 Hz, 1 H), 8.09 (d, *J* = 8.7 Hz, 1  
 10 H), 8.21 (d, *J* = 8.7 Hz, 1 H), 8.24(s, 1 H) , 8.63 (s, 1 H).

11 Ethyl-6-[5,6,7,8-tetrahydro-5,5-dimethyl-8-(O-acetyl)-naphth-7-  
 12 yl]naphth-2-oate  
 13 (Compound B10)

14 To a cold (0 °C) solution of 61 mg (0.16 mmol) of ethyl-6-  
 15 [5,6,7,8-tetrahydro-5,5-dimethyl-8-hydroxy)-naphth-7-yl]naphth-2-oate  
 16 (Compound B4) in 2.0 mL of methylene chloride stirring under  
 17 argon at 0°C was added successively, 76 mg (0.10 mL, 0.72 mmol) of  
 18 triethylamine, 0.22 g (0.20 mL, 2.8 mmol) of acetylchloride and 7  
 19 mg (0.06 mmol) of 4-dimethylaminopyridine. The reaction was  
 20 stirred at room temperature for 90 h, diluted with water, and  
 21 extracted with CH<sub>2</sub>Cl<sub>2</sub> (2x). The combined organic layer was washed  
 22 with brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo* . The title  
 23 compound was obtained as an oil after flash chromatography using  
 24 silica, 10 % ethyl acetate in hexane.

25 <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ\_1.31 (s, 3 H), 1.43 (s, 3 H), 1.46  
 26 (t, 3 H, *J* = 7.1 Hz), 1.67-1.72 (m, 1 H), 1.94-2.12 (m, 3 H), 2.12  
 27 (s, 3 H), 4.46 (q, *J* = 7.1 Hz, 2H), 6.06 (t, *J* = 4.4 Hz, 1 H), 7.51  
 28 (d, *J* = 8.2 Hz, 1 H), 7.61 (d, *J* = 2.0 Hz, 1 H), 7.67 (dd, *J* = 2.0,

1 8.2 Hz, 1 H), 7.78 (dd  $J = 1.7, 8.6$  Hz, 1 H), 7.93 (d,  $J = 8.6$  Hz, 1  
 2 H), 8.01 (d,  $J = 8.7$  Hz, 1 H), 8.04 (s, 1 H), 8.09 (dd,  $J = 1.7, 8.7$   
 3 Hz, 1 H), 8.62 (s, 1 H).

4 Ethyl -6-[5,5-dimethyl-5,6-dihydro--naphthlen-8(7H)-anti-(O-  
 5 methyl-oxime)-2-yl]-naphthalen-2-oate (Compound B11)

6 A solution of 29 mg (0.08 mmol) of ethyl-6-[5,5-dimethyl-5,6-  
 7 dihydro-naphthalen-8(7H) -one-2-yl]-naphthalen-2-oate  
 8 (Compound B6), 27 mg (0.32 mmol) of methoxylamine  
 9 hydrochloride and 68 mg (0.5 mmol) of sodium acetate in 2.0 mL  
 10 of EtOH and 0.5 mL of tetrahydrofuran was heated at 50 °C for  
 11 18 h. An additional 27 mg of methoxylamine hydrochloride was  
 12 added and the mixture refluxed for another 2 h. The mixture was  
 13 concentrated *in vacuo*. The residue was diluted with water and  
 14 extracted with EtOAc (2 x). The combined organic layer was dried  
 15 over  $\text{MgSO}_4$ , and concentrated *in vacuo*.. Flash chromatography  
 16 (silica, 5 % ethyl acetate in hexanes) of the crude material  
 17 afforded the title compound as a solid.

18  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  1.35 (s, 6 H), 1.46 (t,  $J = 7.1$  Hz,  
 19 3 H), 1.77 (t,  $J = 6.9$  Hz, 2 H), 2.84 (t,  $J = 6.9$  Hz, 2 H), 4.04 (s,  
 20 3H), 4.45 (q,  $J = 7.1$  Hz, 2H), 7.47 (d,  $J = 8.2$  Hz, 1 H), 7.67 (dd,  
 21  $J = 2.1, 8.2$  Hz, 1 H), 7.83 (dd,  $J = 1.8, 8.5$  Hz, 1 H), 7.94 (d,  $J =$   
 22 8.6 Hz, 1 H), 8.02 (d,  $J = 8.6$  Hz, 1 H), 8.07-8.10 (m, 2 H), 8.34 (d,  
 23  $J = 2.1$  Hz, 1 H), 8.63 (s, 1 H).

24 6-[5,5-Dimethyl-5,6-dihydro--naphthlen-8(7H)-anti-(O-methyl-oxime)-  
 25 2-yl]-2-naphthoic acid (Compound B12)

26 Employing the same general procedure as for the preparation of  
 27 (E)-4-[2-(5,6,7,8-tetrahydro-5,5-dimethyl-8-anti-(O-methybxime)-2-  
 28 naphthalenyl)ethenyl]-benzoic acid (Compound A4) 22 mg (0.06



1 mmol) of ethyl -6-[5,5-dimethyl-5,6-dihydro--naphthlen-8(7H)-*anti*-  
 2 (O-methyl-oxime)-2-yl]-naphthalen-2-oate (Compound B11) was  
 3 converted into the title compound (white solid).

4 <sup>1</sup>H NMR (DMSO-D6, 300 MHz): δ 1.30 (s, 6 H), 1.72 (t, *J* =  
 5 6.9 Hz, 3 H), 2.78 (t, *J* = 6.9 Hz, 2 H), 3.97 (s, 3 H), 7.59 (d, *J* =  
 6 8.2 Hz, 1 H), 7.81 (dd, *J* = 2.1, 8.2 Hz, 1 H), 7.89 (dd, *J* = 1.8,  
 7 8.7 Hz, 1 H), 8.00 (dd, *J* = 1.7, 8.6 Hz, 1 H), 8.12 (d, *J* = 8.7 Hz,  
 8 1 H), 8.21-8.26 (m, 3 H), 8.64 (s, 1 H).

9 (5,6,7,8-Tetrahydro-5,5-dimethylnaphth-2-yl)boronic acid  
 10 (Compound B13)

11 To a cold (-78 °C) solution of 2.02 g (8.4 mmol) of 6-bromo-  
 12 1,2,3,4-tetrahydro-1,1-dimethylnaphthalene in 11.0 mL of toluene,  
 13 was added 4.6 g (6.8 mL, 10.9 mmol, 1.6 M in hexane) of *n*-BuLi.  
 14 The resulting solution was stirred at -78 °C for 45 min. and then  
 15 2.40 g (3.0 mL, 12.7 mmol) of triisopropylborate was dropwise  
 16 added and the reaction stirred at room temperature for 12 h. The  
 17 reaction was then diluted with 10% HCl, and extracted with ether  
 18 (2 x). The combined organic layer was washed with brine, dried  
 19 over MgSO<sub>4</sub>, and concentrated *in vacuo* to give an oil.  
 20 Recrystallization from hexane afforded the title compound as a  
 21 white solid.

22 <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 1.34 (s, 6 H), 1.71 (m, 2 H), 1.87 (m,  
 23 2 H), 1.89 (t, *J* = 6.3 Hz, 2 H), 7.47 (d, *J* = 7.8 Hz, 1 H), 7.89 (s,  
 24 1 H), 7.99 (d, *J* = 7.8 Hz, 1 H).

25 (5,5-Dimethyl-8-(*t*-butyldimethylsilyloxy)-5,6,7,8-tetrahydro-naphth-2-  
 26 yl)boronic acid (Compound B14)

27 Employing the same general procedure as for the preparation  
 28 of 1,2,3,4-tetrahydro-1,1-dimethylnaphthyl-6-boronic acid

1 (Compound B13) 12.40 g (34 mmol) of 6-bromo-1,2,3,4-  
 2 tetrahydro-1,1-dimethyl-4-(t-butyldimethylsilyloxy)naphthalene  
 3 (Compound B15) was converted into the title compound using  
 4 18.4 g (27.0 mL, 43 mmol, 1.6 M in hexane) of n-BuLi and 9.37 g  
 5 (11.50 mL, 50 mmol) of trisopropylborate.

6  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  0.22 (s, 3 H), 0.28 (s, 3 H), 0.98  
 7 (s, 9 H), 1.33 (s, 3 H), 1.38 (s, 3 H), 1.62-2.09 (m, 4 H), 4.87 (m,  
 8 1 H), 7.39 (d,  $J$  = 7.8 Hz, 1 H), 8.07 (d,  $J$  = 7.8 Hz, 1 H), 8.29  
 9 (s, 1 H).

10 2-(5,6,7,8-tetrahydro-5,5-dimethyl-8-(t-  
 11 butyldimethylsilyloxy)naphthyl)bromide (Compound B15)

12 To a solution of 10.61 g (42 mmol) of 6-bromo-1,2,3,4-  
 13 tetrahydro-1,1-dimethyl-4-hydroxynaphthalene in 100 mL of  
 14 methylene chloride stirring at 0°C under argon, was added 5.23 g  
 15 (7.20 mL, 52 mmol) of triethylamine, 0.55 g (4.5 mmol) of 4-  
 16 dimethylaminopyridine, and 7.71 g (51 mmol) of t-  
 17 butyldimethylsilyl chloride consecutively. The resulting solution  
 18 was stirred at 0°C to room temperature for 90 hours. The  
 19 reaction was then diluted with water, and extracted with  
 20 methylene chloride (2 x), the organic layers dried over  $\text{Na}_2\text{SO}_4$ ,  
 21 and concentrated *in vacuo* to give an oil. Purification was done  
 22 using flash chromatography (silica, 4% ethyl acetate in hexane) to  
 23 give the title compound as an oil.

24  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  0.15 (s, 3H), 0.18 (s, 3H), 0.95  
 25 (s, 9H); 1.25 (s, 3H), 1.26 (s, 3H), 1.61-2.03 (m, 4H), 4.67 (m, 1H),  
 26 7.13 (d,  $J$  = 8.5 Hz, 1H), 7.30 (dd,  $J$  = 2.1, 8.5 Hz, 1H), 7.51 (d,  $J$   
 27 = 2.1 Hz, 1H).

28 4,4-Dimethyl-7-acetyl-3,4-dihydronaphthalen-1(2H)-one

1 (Compound C1)

2 A solution of 4,4-dimethyl-7-bromo-3,4-dihydronaphthalen-  
3 1(2H)one (Compound G) (1.78 g, 7 mmol), 1-ethoxyvinyltributyltin  
4 (EVTB) (3.3 g, 9.12 mmol),

5 bis(triphenylphosphine)palladium(II)chloride (260 mg, 0.23 mmol)  
6 in THF (25 mL) was refluxed for 24 h under argon atmosphere.

7 To the reaction, additional EVTB (1.5 g, 4.1 mmol) and  
8 bis(triphenylphosphine)palladium(II)chloride (200 mg, 0.2 mmol)  
9 were added and the mixture was and refluxed for an additional 24  
10 h. The reaction mixture was cooled to room temperature and  
11 10% hydrochloric acid (10 ml) was added. After 10 min, the  
12 mixture was extracted with ether (3 X 50 mL), the combined  
13 organic layer was washed with water (10 mL), 10%  
14 sodiumbicarbonate (10 mL), brine (10 mL), dried with magnesium  
15 sulfate. Solvent was removed under reduced pressure, and after  
16 purification by flash chromatography the title compound was  
17 obtained as a white solid.

18  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) :  $\delta$  1.38 (s, 6H), 2.02 (t,  $J = 6.54$  Hz, 2H), 2.73  
19 (t,  $J = 6.54$  Hz, 2H), 7.31 (d,  $J = 8.43$  Hz, 1H), 7.63 (dd,  $J =$   
20 2.20, 8.43 Hz, 1H), 8.13 (d,  $J = 2.20$  Hz, 1H).

21 Ethyl 3-[4,4-dimethyl-3,4-dihydronaphthalen-1(2H)one-7-yl]but-  
22 2(E)-enoate (Compound C2)

23 To a cold ( $-78^\circ\text{C}$ ) slurry of sodiumhydride (336 mg, 14 mmol)  
24 in THF (10 mL) was added triethylphosphonoacetate (3.58 g, 16  
25 mmol). Cooling was discontinued and the mixture was stirred at  
26 ambient temperature. After 30 min, a solution of 4,4-dimethyl-7-  
27 acetyl-1,2,3,4-tetrahydronaphthalen-1(2H)-one (Compound C1, 800  
28 mg, 3.7 mmol) in THF (4 mL) was added and stirred for 36 h.

1 The reaction mixture was diluted with ether (120 mL), and washed  
 2 with water (10 mL), brine (10 mL), dried with magnesium sulfate.  
 3 Solvent was removed under reduced pressure, chromatographic  
 4 purification gave the title compound as a colorless oil.

5  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) :  $\delta$  1.33 (t,  $J = 7.1$  Hz, 3H), 1.41 (s, 6H), 2.04  
 6 (t,  $J = 7.0$  Hz, 2H), 2.59 (s, 3H), 2.76 (t,  $J = 7.0$  Hz, 2H), 4.23 (q,  
 7  $J = 7.1$  Hz, 2H), 6.19 (s, 1H), 7.44 (d,  $J = 8.3$  Hz, 1H), 7.65 (dd,  $J$   
 8  $= 2.0, 8.3$  Hz, 1H), 8.15 (d,  $J = 2.0$  Hz, 1H).

9 3-[1-Hydroxy-4,4-dimethyl-1,2,3,4,-tetrahydronaphthalen-7-yl]but-  
 10 2(E)-en-1-ol (Compound C3)

11 To a cold ( $-78^\circ\text{C}$ ) solution of ethyl 3-[4,4-dimethyl-1,2,3,4,-  
 12 tetrahydronaphthalen-1(2H)one-7-yl]but-2(E)-enoate (Compound  
 13 C2, 2.7 g, 9.4 mmol) in methylenechloride (20 mL) was added  
 14 diisobutylaluminum hydride (DibAl-H, 1M solution in  
 15 methylenechloride) (45 mL). The reaction was gradually warmed  
 16 to  $-10^\circ\text{C}$ . The reaction was quenched by adding methanol (3  
 17 mL), water (10 mL), 10% hydrochloric acid (40 mL) and stirred  
 18 for 10 min. The mixture was extracted with methylenechloride (3 x  
 19 50 mL). The combined organic layer was washed with water (10  
 20 mL), 10% sodiumbicarbonate (10 mL), brine (10 mL), dried with  
 21 magnesium sulfate. Solvent was removed under reduced pressure  
 22 to obtain the title compound as a white solid.

23  $^1\text{H}$ NMR ( $\text{CDCl}_3$ ) : d 1.24 (s, 3H), 1.31 (s, 3H), 1.57-1.70 (m, 2H),  
 24 1.82-1.96 (m, 2H), 2.03 (s, 3H), 4.29 (d,  $J = 6.6$  Hz, 2H), 4.68  
 25 (brs, 1H), 5.95 (t,  $J = 6.6$  Hz, 1H), 7.28 (brs, 2H), 7.48 (s, 1H).

26 3-[4,4-Dimethyl-3,4,-dihydronaphthalen-1(2H)one-7-yl]but-2(E)-en-  
 27 al (Compound C4)

28 To a solution of 3-[1-hydroxy-4,4-dimethyl-1,2,3,4,-

1 tetrahydronaphthalen-7-yl]but-2(E)-en-1-ol (Compound C3, 1.5 g,  
2 6.1 mmol) in dichloromethane (35 mL) was added manganese  
3 dioxide (9 g, 106 mmol) in two portions and stirred at room  
4 temperature for 48 h. After filtering out the manganese dioxide  
5 and removing the solvent under reduced pressure the product was  
6 isolated as a white solid.  
7  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.41 (s, 6H), 2.03 (t,  $J = 6.4$  Hz, 2H), 2.58  
8 (s, 3H), 2.75 (t,  $J = 6.4$  Hz, 2H), 6.41 (d,  $J = 7.7$  Hz, 1H), 7.48 (d,  
9  $J = 8.31$ , 1H), 7.71 (dd,  $J = 2.2, 8.31$  Hz, 1H), 8.20 (d,  $J = 2.2$   
10 Hz), 10.18 (d,  $J = 7.7$  Hz, 1H).

1 Ethyl 7-[4,4-dimethyl-3,4-dihydronaphthalen-1(2H)one-7-yl]-3,7-  
 2 dimethyl-hept-2(E), 4(E), 6(E)trienoate (Compound C5)

3 To a cold (-78 °C) solution of diethyl-(E)-3-ethoxycarbonyl-2-  
 4 methylallylphosphonate in THF was added n-BuLi (1.6 mmol  
 5 solution in hexanes, 2.2 mL, 3.5 mmol) followed by 3-[4,4-  
 6 dimethyl-1,2,3,4-tetrahydronaphthalen-1(2H)one-7-yl]but-2(E)-en-  
 7 al (Compound C4, 300 mg, 1.24 mmol) in THF (2 mL). The  
 8 mixture was stirred for 16 h at -78 °C. The mixture was treated  
 9 with water and extracted with ether (3 X 40 mL). The combined  
 10 organic layer was washed with water (10 mL), brine (10 mL) and  
 11 dried with MgSO<sub>4</sub>. Solvent was removed under reduced  
 12 pressure, the crude product was purified by column  
 13 chromatography, followed by HPLC to give the title compound as  
 14 a solid.

15 <sup>1</sup>H NMR (CDCl<sub>3</sub>) : δ 1.30 (t, J = 7.1 Hz, 3H), 1.40 (s, 6H), 2.03  
 16 (t, J = 6.8 Hz, 2H), 2.26 (s, 3H), 2.38 (s, 3H), 2.75 (t, J = 6.8 Hz,  
 17 2H), 4.20 (q, J = 7.1 Hz, 2H), 5.82 (s, 1H), 6.41 (s, J = 15.0 Hz,  
 18 1H), 6.64 (d, J = 11.0 Hz, 1H), 7.01 (dd, J = 11.0, 15.0 Hz, 1H),  
 19 7.41 (d, J = 8.2 Hz, 1H), 7.66 (dd, J = 2.0, 8.2 Hz, 1H), 8.14 (d, J  
 20 = 2.0 Hz).

21 4,4-Dimethyl-7-acetyl-1-phenylthio-3,4-dihydronaphthalene  
 22 (Compound C7)

23 Employing the procedure used for the preparation of 4,4-  
 24 dimethyl-7-acetyl-3,4-dihydronaphthalen-1(2H)-one (Compound  
 25 C1) 1.2 g, (3.5 mmol) of 4,4-dimethyl-7-Bromo-1-phenylthio-3,4-  
 26 dihydronaphthalene (Compound A35) was converted to the title  
 27 compound.

28 <sup>1</sup>H NMR (CDCl<sub>3</sub>) : δ 1.35 (s, 6H), 2.42 (d, J = 4.8 Hz, 2H), 2.43

1 (s, 3H), 6.59 (t, J = 4.8 Hz, 1H), 7.10-7.27 (m, 4H), 7.32 (d, J =  
2 8.5 Hz, 1H), 7.40 (d, J = 8.1 Hz, 1H), 7.82 (dd, J = 1.9, 8.1 Hz,  
3 1H), 8.18 (d, J = 1.9 Hz, 1H).

4 3-[4,4-Dimethyl-1-phenylthio-3,4-dihydronaphthalen-7-yl]but-2-  
5 en(E)-nitrile (Compound C8)

6 Employing the procedure used for the preparation of ethyl 3-  
7 [4,4-dimethyl-3,4-dihydronaphthalen-1(2H)one-7-yl]but-2(E)-  
8 enoate (Compound C2) instead using  
9 diethylcyanomethylphosphonate (1.77 g, 10 mmol), sodium hydride  
10 (220 mg, 9 mmol) and 4,4-dimethyl-7-acetyl-1-phenylthio-3,4-  
11 dihydronaphthalene (Compound C7, 924 mg, 3 mmol) was  
12 converted to the title compound.  
13 <sup>1</sup>H NMR (CDCl<sub>3</sub>) : δ 1.34 (s, 6H), 2.30 (s, 3H), 2.42 (d, J = 4.6  
14 Hz, 2H), 5.38 (s, 1H), 6.61 (t, J = 4.6 Hz, 1H), 7.10-7.37 (m, 7H),  
15 7.69 (d, J = 1.9 Hz, 1H).

1 3-[4,4-Dimethyl-1-phenylthio-3,4-dihydronaphthalen-7-yl]but-2-  
 2 en(E)-aldehyde (Compound C9)

3 To a cold (-78 °C) solution of 3-[4,4-dimethyl-1-phenylthio-3,4-  
 4 dihydronaphthalen-7-yl]but-2-en(E)-nitrile (Compound C8, 400  
 5 mg, 1.2 mmol), in dichloromethane (10 mL) was added  
 6 diisobutylaluminum hydride (DIBAL-H) (1M solution in  
 7 dichloromethane, 2.5 mL, 2.5 mmol). The reaction was warmed to  
 8 -40 °C gradually over a period of 1 h. Then the reaction was  
 9 quenched by adding methanol (1.5 mL), diluted with ether :  
 10 ethylacetate (1:1, 100 mL), washed with 10% HCl (10 mL), water  
 11 (10 mL), and brine (10 mL). The organic layer was dried  
 12 (MgSO<sub>4</sub>) and the solvent was removed under reduced pressure.  
 13 The title compound was obtained as a colorless oil after silicagel  
 14 chromatography.

15 <sup>1</sup>H NMR (CDCl<sub>3</sub>) : δ 1.36 (s, 6H), 2.40 (d, J = 1.3 Hz, 3H), 2.42  
 16 (d, J = 4.7 Hz, 2H), 6.25 (dd, J = 1.3, 7.9 Hz, 1H), 6.60 (t, J =  
 17 4.7 Hz, 1H), 7.10-7.43 (m, 7H), 7.81 (d, J = 1.9 Hz, 1H), 10.11 (d,  
 18 J = 7.9 Hz, 1H).

19 Ethyl 7-[4,4-dimethyl-1-(phenylthio)-3,4,-dihydronaphthalen-7-yl]-  
 20 3,7-dimethyl-hept-2(E), 4(E), 6(E)trienoate (Compound C10)

21 Employing the procedure used for the preparation of ethyl 7-  
 22 [4,4-dimethyl-3,4,-dihydronaphthalen-1(2H)one-7-yl]-3,7-dimethyl-  
 23 hept-2(E), 4(E), 6(E)trienoate (Compound C5) instead using  
 24 diethyl-(E)-3-ethoxycarbonyl-2-methylallylphosphonate (786 mg, 3  
 25 mmol), n -BuLi (2.8 mmol), 3-[4,4-dimethyl-1-phenylthio-3,4-  
 26 dihydronaphthalen-7-yl]but-2-en(E)-aldehyde (Compound C9, 280  
 27 mg, 0.84 mmol) was converted to the title compound.

28 <sup>1</sup>H NMR (CDCl<sub>3</sub>) : δ 1.32 (t, J = 7.1 Hz, 3H), 1.36 (s, 6H), 2.12



1 (s, 3H), 2.38 (s, 3H), 2.41 (d, J = 4.7 Hz, 2H), 4.20 (q, J = 7.1  
 2 Hz, 2H), 5.82 (s, 1H), 6.29 (d, J = 14.8 Hz, 1H), 6.33 (d, J = 9.9  
 3 Hz, 1H), 6.58 (t, J = 4.7 Hz, 1H), 6.96 (dd, J = 9.9, 14.8 Hz, 1H),  
 4 7.12-7.38 (m, 7H), 7.74 (d, J = 1.7 Hz, 1H).

5 Ethyl 7-[4,4-dimethyl-1-phenylsulfonyl-3,4,-dihydronaphthalen-7-  
 6 yl]-3,7-dimethyl-hept-2(E), 4(E), 6(E)trienoate (Compound C11a)

7 Ethyl 7-[4,4-dimethyl-1-phenylsulfoxide-3,4,-dihydronaphthalen-7-  
 8 yl]-3,7-dimethyl-hept-2(E), 4(E), 6(E)trienoate (Compound C11b)

9 To a cold (0 °C) solution of ethyl 7-[4,4-dimethyl-1-phenylthio-  
 10 3,4,-dihydronaphthalen-7-yl]-3,7-dimethyl-hept-2(E), 4(E),  
 11 6(E)trienoate (Compound C10, 44 mg, 0.1 mmol) in  
 12 dichloromethane (3 mL) was added m-chloroperoxybenzoic acid  
 13 (approximately 60% concentration, 30 mg, 0.1 mmol). The mixture  
 14 was stirred for 2 h at 0 °C, diluted with dichloromethane (40 mL)  
 15 and washed successively with 10% sodiumbicarbonate (5 mL),  
 16 water (5 mL) and brine (5 mL). The organic layer was dried  
 17 (MgSO<sub>4</sub>) and the solvent was removed under reduced pressure.  
 18 The title compounds were obtained after separation of the mixture  
 19 by silicagel chromatography.

20 Ethyl 7-[4,4-dimethyl-1-phenylsulfonyl-3,4,-dihydronaphthalen-7-  
 21 yl]-3,7-dimethyl-hept-2(E), 4(E), 6(E)trienoate (Compound 11a)  
 22 <sup>1</sup>H NMR (CDCl<sub>3</sub>) : δ 1.23 (s, 6H), 1.31 (t, J = 7.1 Hz, 3H), 2.17  
 23 (s, 3H), 2.39 (s, 3H), 2.51 (d, J = 4.9 Hz, 2H), 4.20 (q, J = 7.1  
 24 Hz, 2H), 5.84 (s, 1H), 6.36 (d, J = 15.1 Hz, 1H), 6.41 (d, J = 13.0  
 25 Hz, 1H), 6.99 (dd, J = 12.0, 15.1 Hz), 1H), 7.27 (d, J = 1.7 Hz,  
 26 1H), 7.34 (dd, J = 1.9, 8.2 Hz, 1H), 7.45-7.60 (m, 4H), 7.93-8.0  
 27 (m, 3H).

28 Ethyl 7-[4,4-dimethyl-1-phenylsulfoxide-3,4,-dihydronaphthalen-7-

1 yl]-3,7-dimethyl-hept-2(E), 4(E), 6(E)trienoate (Compound 11b)  
 2  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) :  $\delta$  1.32 (s, 3H), 1.30 (s, 3H), 1.31 (t,  $J = 7.1$   
 3 Hz, 3H), 2.15 (s, 3H), 2.38 (s, 3H), 2.50 (d,  $J = 4.6$  Hz, 2H), 4.19  
 4 (q,  $J = 7.1$  Hz, 2H), 5.84 (s, 1H), 6.36 (d,  $J = 15.0$  Hz, 1H), 6.39  
 5 (d,  $J = 11.6$  Hz, 1H), 6.90-7.04 (m, 2H), 7.24-7.32 (m, 2H), 7.41-  
 6 7.50 (m 3H), 7.53 (d,  $J = 1.8$  Hz, 1H), 7.74 (dd,  $J = 2.5, 8.0$  Hz,  
 7 2H).

8 Ethyl 7-[4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-hydroxy-7-yl]-  
 9 3,7-dimethyl-hept-2(E), 4(E), 6(E)trienoate (Compound C13)

10 To cold ( $0^\circ\text{C}$ ) solution of ethyl 7-[4,4-dimethyl-3,4,-  
 11 dihydronaphthalen-1(2H)one-7-yl]-3,7-dimethyl-hept-2(E), 4(E),  
 12 6(E)trienoate (Compound C5, 6 mg, 0.02 mmol) in ether (3 mL)  
 13 was added  $\text{ZnBH}_4$  (0.5 M solution in ether, 0.5 mL). The mixture  
 14 was stirred for 30 min. and quenched the with water, diluted with  
 15 ether (30 mL). The organic layer was washed with water (5 mL),  
 16 10% HCl (5 mL), water (5 mL), 10%  $\text{NaHCO}_3$  (5 mL) and brine  
 17 (5 mL). The organic layer was dried with  $\text{MgSO}_4$ , and the solvent  
 18 was removed under reduced pressure to obtain the title compound  
 19 as a white solid.

20  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.26 (s, 3H), 1.30 (t,  $J = 7.1$  Hz, 3H), 1.34  
 21 (s, 3H), 1.58-1.70 (m, 1H), 1.82-1.95 (m, 2H), 2.05-2.15 (m, 1H),  
 22 2.25 (s, 3H), 2.38 (s, 3H), 4.18 (q,  $J = 7.1\text{Hz}$ ), 4.75 (brs, 1H), 5.81  
 23 (s, 1H), 6.37 (d,  $J = 15.1$  Hz, 1H), 6.60 (d,  $J = 11.2$  Hz, 1H), 7.02  
 24 (dd,  $J = 11.2, 15.1$  Hz, 1H), 7.31 (d,  $J = 8.3$  Hz, 1H), 7.39 (dd,  $J$   
 25  $= 2.1, 8.3$  Hz, 1H).

1 Ethyl 7-[4,4-dimethyl-3,4,-dihydronaphthalen-1-  
 2 trifluoromethylsulfonyloxy-7-yl]-3,7-dimethyl-hept-2(E), 4(E),  
 3 6(E)trienoate (Compound C14)

4 To a cold (-78 °C) stirring solution of ethyl 7-[4,4-dimethyl-  
 5 3,4,-dihydronaphthalen-1(2H)one-7-yl]-3,7-dimethyl-hept-2(E),  
 6 4(E), 6(E)trienoate (Compound C5, 190 mg, 0.55 mmol), in THF  
 7 (10 mL) was added sodium bis(trimethylsilyl)amide (1M solution  
 8 in THF, 0.5 mL, 0.5 mmol). After 20 min. 2-*N,N*-  
 9 bis(trifluoromethylsulfonyl)amino-5-chloropyridine (216 mg, 0.6  
 10 mmol) in THF (2 mL) was added, after another 20 min. the  
 11 temperature was increased to -10 °C and the mixture was stirred  
 12 at this temperature for another 20 min. The reaction was  
 13 quenched by adding aqueous NH<sub>4</sub>Cl (10 mL), extracted with ether  
 14 (3 X 30 mL). The combined organic layer was washed successively  
 15 with water (10 mL) and brine (10 mL), dried with MgSO<sub>4</sub>. The  
 16 solvent was removed, and the resulting crude mixture was purified  
 17 by silicagel chromatography and HPLC to afford the title  
 18 compound as a white solid.

19 <sup>1</sup>H NMR (CDCl<sub>3</sub>) : δ 1.31 (t, J = 7.1 Hz, 3H), 1.32 (s, 6H), 2.25  
 20 (s, 3H), 2.39 (s, 3H), 2.43 (d, J = 4.9, 2H), 4.19 (q, J = 7.1 Hz,  
 21 2H), 5.83 (s, 1H), 5.99 (t, J = 4.9 Hz, 1H), 6.40 (d, J = 15.0 Hz,  
 22 1H), 6.57 (d, J = 11.3 Hz, 1H), 7.01 (dd, J = 11.3, 15.0 Hz, 1H),  
 23 7.30 (d, J = 8.0 Hz, 1H), 7.46 (dd, J = 1.9, 8.0 Hz, 1H), 7.47 (d, J  
 24 = 1.9 Hz, 1H).

25 Ethyl 7-[4,4-dimethyl-3,4,-dihydronaphthalen-1-(2-thienyl)-7-yl]-3,7-  
 26 dimethyl-hept-2(E), 4(E), 6(E)trienoate (Compound C15)

27 To a cold (-78 °C) solution of thiophene (252 mg, 3 mmol) in  
 28 THF (2 mL) was added t-BuLi (1.4 M solution in cyclohexane, 2

1 mL, 2.8 mmol) and the mixture was warmed to -30 °C over a  
 2 period of 30 min. The mixture was recooled to -78 °C and a  
 3 solution of zinc chloride (408 mg, 3 mmol) in THF (1 mL) was  
 4 added to it. The white turbid mixture was warmed to ambient  
 5 temperature and stirred for 30 min. This mixture was transferred  
 6 to a flask containing ethyl 7-[4,4-dimethyl-3,4,-dihydronaphthalen-  
 7 1-trifluoromethylsulfonyloxy-7-yl]-3,7-dimethyl-hept-2(E), 4(E),  
 8 6(E)trienoate (Compound C14, 118 mg, 0.25 mmol), palladium  
 9 tetrakis(triphenylphosphine) (250 mg, 0.22 mmol) and THF (1  
 10 mL). The reactants were heated to 50 °C for 3 h. and then the  
 11 reaction was quenched by adding aqueous NH<sub>4</sub>Cl (10 mL). The  
 12 reaction mixture was extracted with ethylacetate (3 X 20 mL). The  
 13 combined organic layer was washed with water (10 mL) and brine  
 14 (10 mL), dried with MgSO<sub>4</sub>. The solvent was removed under  
 15 reduced pressure and the title compound was obtained as pale  
 16 yellow solid after silicagel chromatography.

17 <sup>1</sup>H NMR (CDCl<sub>3</sub>) : δ 1.29 (t, J = 7.1 Hz), 1.33 (s, 6H), 2.18 (s,  
 18 3H), 2.33 (d, J = 4.8 Hz, 2H), 2.36 (s, 3H), 4.17 (q, J = 7.1 Hz,  
 19 2H), 5.79 (s, 1H), 6.21 (t, J = 4.8 Hz, 1H) 6.33 (d, J = 15.1 Hz,  
 20 1H), 6.48 (d, J = 11.5 Hz, 1H), 6.98 (dd, J = 11.5, 15.1 Hz, 1H),  
 21 7.08 (br d, J = 3.4 Hz, 2H), 7.26-7.29 (m, 1H), 7.32-7.41 (m, 2H),  
 22 7.52 (d, J = 1.6 Hz, 1H).

23 Ethyl 7-[4,4-dimethyl-3,4,-dihydronaphthalen-1(2H)-(anti)(O-  
 24 methyl-oxime)-7-yl]-3,7-dimethyl-hept-2(E), 4(E), 6(E)trienoate  
 25 (Compound C16)

26 To a solution of ethyl 7-[4,4-dimethyl-3,4,-dihydronaphthalen-  
 27 1(2H)one-7-yl]-3,7-dimethyl-hept-2(E), 4(E), 6(E)trienoate  
 28 (Compound C5, 25 mg, 0.07 mmol) in ethanol (2 mL) and THF (2

1 mL), was added sodium acetate trihydrate (103 mg, 0.75 mmol)  
2 followed by methoxylamine hydrochloride (42 mg, 0.5 mmol).  
3 The mixture was stirred at ambient temperature for 16 h and  
4 diluted with ether (60 mL). The ether layer was washed  
5 successively with 10% NaHCO<sub>3</sub> (5 mL), water (5 mL) and brine  
6 (10 mL). The organic layer was dried with MgSO<sub>4</sub> and the  
7 solvent was removed under reduced pressure. After purification  
8 by chromatography on silicagel the title compound was obtained  
9 as a white solid .  
10 <sup>1</sup>H NMR (CDCl<sub>3</sub>) : δ 1.29 (s, 6H), 1.30 (t, J = 7.1 Hz, 3H), 1.72  
11 (t, J = 7.0 Hz, 2H), 2.27 (s, 3H), 2.39 (s, 3H), 2.80 (t, J = 7.0 Hz,  
12 2H), 4.03 (s, 3H), 4.18 (q, J = 7.1 Hz, 2H), 5.82 (s, 1H), 6.40 (d, J  
13 = 15.0 Hz, 1H), 6.60 (2, J = 11.0 Hz, 1H), 7.03 (dd, J = 11.0,  
14 15.0 Hz, 1H), 7.33 (d, J = 8.3 Hz, 1H), 7.44 (dd, J = 2.1 Hz, 8.3  
15 Hz, 1H), 8.07 (d, J = 2.1 Hz, 1H).

1 Ethyl 7-[4,4-dimethyl-3,4,-dihydronaphthalen-1(2H)-  
 2 (anti)(carbethoxymethylenyl)-7-yl]-3,7-dimethyl-hept-2(E), 4(E),  
 3 6(E)trienoate (Compound C17a)

4 Ethyl 7-[4,4-dimethyl-3,4,-dihydronaphthalen-1(2H)-  
 5 (syn)(carbethoxymethylenyl)-7-yl]-3,7-dimethyl-hept-2(E), 4(E),  
 6 6(E)trienoate (Compound C17b)

7 To a cold (-78 °C) slurry of sodium hydride (24 mg, 1 mmol)  
 8 in THF (3 mL) was added triethylphosphonoacetate (300 mg, 1.4  
 9 mmol). The mixture was stirred for 30 min. at 0 °C. To this  
 10 mixture a solution of ethyl 7-[4,4-dimethyl-3,4,-dihydronaphthalen-  
 11 1(2H)one-7-yl]-3,7-dimethyl-hept-2(E), 4(E), 6(E)-trienoate  
 12 (Compound C5, 50 mg, 0.15 mmol) in THF (2 mL) was added and  
 13 stirred at ambient temperature for 48 h. The reaction was  
 14 quenched by adding water (5 mL) and extracted with ethyl acetate  
 15 (3 X 30 mL). The combined organic layer was washed with water  
 16 (5 mL), brine (5 mL) and dried (MgSO<sub>4</sub>). The solvent was  
 17 removed under reduced pressure and the title compounds were  
 18 obtained after silicagel chromatography and HPLC separation.  
 19 Ethyl 7-[4,4-dimethyl-3,4,-dihydronaphthalen-1(2H)-  
 20 (anti)(carbethoxymethylenyl)-7-yl]-3,7-dimethyl-hept-2(E), 4(E),  
 21 6(E)trienoate (Compound 17a)  
 22 <sup>1</sup>H NMR (CDCl<sub>3</sub>) : δ 1.30 (s, 6H), 1.30 (t, J = 7.1Hz, 3), 1.34 (t,  
 23 J = 7.1 Hz, 3H), 1.73 (t, J = 6.6 Hz, 2H), 2.26 (s, 3H), 2.38 (s,  
 24 3H), 3.24 (t, J = 6.6 Hz, 2H), 4.13-4.28 (m, 4H), 5.82 (s, 1H), 6.31  
 25 (s, 1H), 6.40 (d, J = 15.0 Hz, 1H), 6.57 (d, J = 11.5 Hz, 1H), 7.01  
 26 (dd, J = 11.5, 15.0 Hz, 1H), 7.35 (d, J = 8.3 Hz, 1H), 7.46 (dd, J  
 27 = 1.9, 8.3 Hz, 1H), 7.66 (d, J = 1.9 Hz, 1H).

28 Ethyl 7-[4,4-dimethyl-3,4,-dihydronaphthalen-1(2H)-

1 (*syn*)(carbethoxymethylenyl)-7-yl]-3,7-dimethyl-hept-2(E), 4(E),  
2 6(E)trienoate (Compound C17b)

3  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) :  $\delta$  1.25 (t,  $J$  = 7.1 Hz, 3H), 1.28 (t,  $J$  = 7.1  
4 Hz, 3H), 1.32 (s, 6H), 1.83 (t,  $J$  = 6.5 Hz, 2H), 2.23 (s, 3H), 2.38  
5 (s, 3H), 2.54 (t,  $J$  = 6.5 Hz, 2H), 4.12-4.25 (m, 4H), 5.81 (s, 2H),  
6 6.38 (d,  $J$  = 15.1 Hz, 1H), 6.57 (d,  $J$  = 11.0 Hz, 1H), 7.01 (dd,  $J$   
7 = 11.0, 15.1 Hz, 1H), 7.30 (d,  $J$  = 8.3 Hz, 1H), 7.46 (dd,  $J$  = 1.9,  
8 8.3 Hz, 1H), 7.72 (d,  $J$  = 1.9 Hz, 1H).

9 7-[4,4-Dimethyl-1,2,3,4,-tetrahydronaphthalen-1-hydroxy-7-yl]-3,7-  
10 dimethyl-hept-2(E), 4(E), 6(E)trienoic acid (Compound C19)

11 To a solution of ethyl 7-[4,4-dimethyl-1,2,3,4,-  
12 tetrahydronaphthalen-1-hydroxy-7-yl]-3,7-dimethyl-hept-2(E), 4(E),  
13 6(E)trienoate (Compound C13, 35 mg, 0.1 mmol) in THF (3 mL)  
14 and methanol (1 mL), was added lithiumhydroxide (1M solution in  
15 water, 0.3 mL, 0.3 mmol) and warmed to 60 oC for 6 h. The  
16 reaction mixture was diluted with ether : ethylacetate (1:1, 40 mL),  
17 acidified with 10% aqueous HCl to pH 6. The organic layer was  
18 washed with water (5 mL), brine (5 mL) and dried ( $\text{MgSO}_4$ ), and  
19 the solvent was removed under reduced pressure. After  
20 purification by preparative TLC the title compound was obtained  
21 as a pale yellow solid .

22  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) :  $\delta$  1.26 (s, 3H), 1.34 (s, 3H), 1.55-1.65 (m,  
23 1H), 1.70-2.10 (m, 3H), 2.27 (s, 3H), 2.40 (s, 3H), 4.77 (t,  $J$  = 5.6  
24 Hz, 1H), 5.84 (s, 1H), 6.41 (d,  $J$  = 15.1 Hz, 1H), 6.62 (d,  $J$  = 11.1  
25 Hz, 1H), 7.08 (dd,  $J$  = 11.1, 15.1 Hz, 1H), 7.32 (d,  $J$  = 8.3 Hz,  
26 1H), 7.40 (dd,  $J$  = 1.9, 8.3 Hz, 1H), 7.57 (d,  $J$  = 1.9 Hz, 1H).

27 7-[4,4-Dimethyl-3,4,-dihydronaphthalen-1-(2-thienyl)-7-yl]-3,7-  
28 dimethyl-hept-2(E), 4(E), 6(E)trienoic acid (Compound C20)

1       Employing the procedure used for the preparation of 7-[4,4-  
2       dimethyl-1,2,3,4,-tetrahydronaphthalen-1-hydroxy-7-yl]-3,7-  
3       dimethyl-hept-2(E), 4(E), 6(E)trienoic acid (Compound C19), 20  
4       mg (0.05 mmol) of ethyl 7-[4,4-dimethyl-3,4,-dihydronaphthalen-1-  
5       (2-thienyl)-7-yl]-3,7-dimethyl-hept-2(E), 4(E), 6(E)trienoate  
6       (Compound C15) was converted to the title compound.  
7       <sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) : δ 1.30 (s, 6H), 2.19 (s, 3H), 2.32 (d, J =  
8       4.8 Hz, 2H), 2.35 (s, 3H), 5.84 (s, 1H), 6.22 (t, J = 4.8 Hz, 1H),  
9       6.47 (d, J = 15.1 Hz, 1H), 6.58 (d, J = 11.0 Hz, 1H), 7.05-7.18 (m,  
10      3H), 7.38-7.55 (m, 4H).



1 Ethyl 7-[4,4-dimethyl-3,4,-dihydronaphthalen-1-cyano-7-yl]-3,7-  
2 dimethyl-hept-2(E), 4(E), 6(E)trienoate (Compound C21)

3 To a solution of ethyl 7-[4,4-dimethyl-3,4,-dihydronaphthalen-1-  
4 trifluoromethylsulfonyloxy-7-yl]-3,7-dimethyl-hept-2(E), 4(E),  
5 6(E)trienoate (Compound C14, 87 mg, 0.18 mmol) in THF (10  
6 mL) were added tetrakis(triphenylphosphine)palladium (10 mg,  
7 0.01 mmol) and zinc cyanide (42 mg, 0.36 mmol). The mixture was  
8 heated to 50 °C for 1h. Additional quantities of  
9 tetrakis(triphenylphosphine)palladium (10 mg, 0.01 mmol) and  
10 zinc cyanide (42 mg, 0.36 mmol) were added and the mixture  
11 heated to 50 °C for another 1h. The reaction was quenched with  
12 water (5 mL), extracted with ethyl acetate (2 X 20 mL), and the  
13 combined organic layer was washed with water, followed by brine.  
14 The organic layer was dried (MgSO<sub>4</sub>) and solvent removed under  
15 reduced pressure. After silicagel chromatography the title  
16 compound was isolated as a solid .  
17 <sup>1</sup>H NMR (CDCl<sub>3</sub>) : δ 1.29 (s, 6H), 1.30 (t, J = 7.1 Hz, 3H), 2.26  
18 (s, 3H), 2.39 (s, 3H), 2.41 (d, J = 4.8 Hz, 2H), 4.18 (q, J = 7.1  
19 Hz, 2H), 5.83 (s, 1H), 6.41 (d, J = 15.0 Hz, 1H), 6.61 (d, J = 11.0  
20 Hz, 1H), 6.87 (t, J = 4.8 Hz, 1H), 7.01 (dd, J = 11.0, 15.0 Hz,  
21 1H), 7.32 (d, J = 8.2 Hz, 1H), 7.44 (dd, J = 2.0, 8.2 Hz, 1H), 7.57  
22 (d, J = 2.0 Hz, 1H).

1 Ethyl 7-[4,4-dimethyl-3,4-dihydro-1(2H)-*syn*-(O-ethyl oxime)-  
 2 naphth-7-yl]3,7-dimethyl-hepta-2(E),4(E),6(E)-trienoate  
 3 (Compound 22a)

4 Ethyl 7-[4,4-dimethyl-3,4-dihydro-1(2H)-*anti*-(O-ethyl oxime)-  
 5 naphth-7-yl]3,7-dimethyl-hepta-2(E),4(E),6(E)-trienoate  
 6 (Compound C22b)

7 To a solution of ethyl 7-[4,4-dimethyl-3,4-dihydronaphthalen-  
 8 1(2H)one-7-yl]3,7-dimethyl-hepta-2(E),4(E),6(E)-trienoate  
 9 (Compound C5, 128 mg, 0.4 mmol) in THF (10 mL) and ethanol  
 10 (10 mL), was added O-ethylhydroxylamine hydrochloride (280  
 11 mg, 2.8 mmol), sodium acetate trihydrate (600 mg, 4.4 mmol)  
 12 and the mixture was stirred at ambient temperature for 80 h.  
 13 The reaction mixture was diluted with ethyl acetate (50 mL) and  
 14 washed with water (10 mL) and brine (50 mL). The organic phase  
 15 was dried over MgSO<sub>4</sub> and then concentrated *in vacuo* to a yellow  
 16 oil. Purification by column chromatography (silica, 10% EtOAc-  
 17 hexane) followed by HPLC separation (partisil 10, 10% EtOAc-  
 18 hexane) afforded the title compounds as white solid in the ratios  
 19 of 1 (*syn*) : 7 (*anti*).

20 Ethyl 7-[4,4-dimethyl-3,4-dihydro-1(2H)-*syn*-(O-ethyl oxime)-  
 21 naphth-7-yl]3,7-dimethyl-hepta-2(E),4(E),6(E)-trienoate  
 22 (Compound C22a)

23 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.27-1.39 (m, 12H), 1.88 (t, J = 6.3Hz, 2H),  
 24 2.25 (s, 3H), 2.39 (s, 3H), 2.56 (t, J = 6.5Hz, 2H), 4.19 (m, 4H),  
 25 5.81 (s, 1H), 6.34 (d, J = 15.0Hz, 1H), 6.57 (d, J = 11.0Hz, 1H),  
 26 7.03 (dd, J = 11.4, 15.0Hz, 1H), 7.36 (d, J = 8.4Hz, 1H), 7.46 (dd,  
 27 J = 2.0, 8.6Hz, 1H), 8.65 (d, J = 2.0Hz, 1H).

28 Ethyl 7-[4,4-dimethyl-3,4-dihydro-1(2H)-*anti*-(O-ethyl oxime)-

1 naphth-7-yl]3,7-dimethyl-hepta-2(E),4(E),6(E)-trienoate

2 (Compound C22b)

3  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.28-1.31 (m, 9H), 1.36 (t,  $J = 8.2\text{Hz}$ , 3H),

4 1.73 (t,  $J = 6.9\text{Hz}$ , 2H) 2.27 (s, 3H), 2.40 (s, 3H), 2.82 (t,  $J =$

5 6.9Hz, 2H), 4.20 (q,  $J = 7.2\text{Hz}$ , 2H), 4.3 (q,  $J = 7.1\text{Hz}$ , 2H), 5.83

6 (s, 1H), 6.38 (d,  $J = 15.1\text{Hz}$ , 1H), 6.59 (d,  $J = 11.0\text{Hz}$ , 1H), 7.03

7 (dd,  $J = 11.2, 15.1\text{Hz}$ , 1H), 7.32 (d,  $J = 8.3\text{Hz}$ , 1H), 7.42 (dd,  $J =$

8 2.1, 8.2Hz, 1H), 8.09 (d,  $J = 2.0\text{Hz}$ , 1H).

9 7-[4,4-dimethyl-3,4-dihydro-1(2H)-*syn*-(O-ethyl oxime)-naphth-7-  
10 yl]3,7-dimethyl-hepta-2(E),4(E),6(E)-trienoic acid (Compound  
11 C24)

12 To a solution of ethyl 7-[4,4-dimethyl-3,4-dihydro-1(2H)-*syn*-

13 (O-ethyl oxime)-naphth-7-yl]3,7-dimethyl-hepta-2(E),4(E),6(E)-

14 trienoate (Compound C22a, 7.8 mg, 0.02 mmol) in THF (1 mL)

15 and ethanol (1 mL), was added 1M lithium hydroxide (0.08 mL,

16 0.08 mmol) and the mixture was stirred at ambient temperature

17 for 8 days. Thereafter the reaction mixture was diluted with  $\text{Et}_2\text{O}$

18 : EtOAc (1:1, 10ml) and acidified with 10% HCl to pH 4. The

19 organic layer was washed with water (5 mL), brine (10 mL), dried

20 ( $\text{MgSO}_4$ ) and the solvent was removed under reduced pressure.

21 Recrystallization from EtOAc/hexane gave the title compound as a  
22 pale yellow solid.

23  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.32 (s, 6H), 1.36 (t,  $J = 7.1\text{Hz}$ , 3H), 1.88(t,

24  $J = 8.7\text{Hz}$ , 2H), 2.25 (s, 3H), 2.39 (s, 3H), 2.55 (t,  $J = 6.5\text{Hz}$ , 2H),

25 4.20 (q,  $J = 7.0\text{Hz}$ , 2H), 5.84 (s, 1H), 6.36 (d,  $J = 15.0\text{Hz}$ , 1H),

26 6.58 (d,  $J = 11.0\text{Hz}$ , 1H), 7.03 (dd,  $J = 11.2, 15.1\text{Hz}$ , 1H), 7.36 (d,

27  $J = 8.4\text{Hz}$ , 1H), 7.47 (dd,  $J = 2.0, 8.6\text{Hz}$ , 1H), 8.65 (d,  $J = 2.0\text{Hz}$ ,

28 1H).

1 7-[4,4-dimethyl-3,4-dihydro-1(2H)-anti-(O-ethyl oxime)-naphth-7-  
 2 yl]3,7-dimethyl-hepta-2(E),4(E),6(E)-trienoic acid (Compound  
 3 C25)

4 To a solution of ethyl 7-[4,4-dimethyl-3,4-dihydro-1(2H)-anti-  
 5 (O-ethyl oxime)-naphth-7-yl]3,7-dimethyl-hepta-2(E),4(E),6(E)-  
 6 trienoate (Compound C22b, 40 mg, 0.1 mmol) in THF (2 mL)  
 7 and ethanol (2 mL), was added 1M lithium hydroxide (2 mL, 2  
 8 mmol) and the mixture was stirred at ambient temperature for 3  
 9 days and thereafter at 50° C for 8h. The reaction mixture was  
 10 diluted with Et<sub>2</sub>O : EtOAc (1:1, 10ml), and then acidified with  
 11 10% HCl to pH 4. The organic layer was washed with water (5  
 12 mL), brine (10 ml), dried (MgSO<sub>4</sub>) and the solvent was removed  
 13 under reduced pressure. Recrystallization from EtOAc/hexane  
 14 gave the title compound as a pale yellow solid.

15 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.30 (s, 6H), 1.36 (t, J = 7.0Hz, 3H), 1.73 (t,  
 16 J = 7.0Hz, 2H) 2.28 (s, 3H), 2.41 (s, 3H), 2.81 (t, J = 6.9Hz, 2H),  
 17 4.25 (q, J = 7.1Hz, 2H), 5.86 (s, 1H), 6.41 (d, J = 15.0Hz, 1H),  
 18 6.60 (d, J = 11.4Hz, 1H), 7.03 (dd, J = 11.4, 15.1Hz, 1H), 7.32 (d,  
 19 J = 8.4Hz, 1H), 7.42 (dd, J = 2.1, 8.4Hz, 1H), 8.09 (d, J = 2.0Hz,  
 20 1H).

21 (-/+ )Ethyl 7-[4,4-dimethyl-1,2,3,4-tetrahydro-1-(O-  
 22 methoxymethyl)-naphth-7-yl]3,7-dimethyl-hepta-2(E),4(E),6(E)-  
 23 trienoate (Compound C26)

24 To a solution of (-/+ )ethyl 7-[4,4-dimethyl-1,2,3,4-tetrahydro-  
 25 1-hydroxy -naphth-7-yl]3,7-dimethyl-hepta-2(E),4(E),6(E)-trienoate  
 26 (Compound C13, 67 mg, 0.19 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) were  
 27 added *N,N*-diisopropylethylamine (91 mg, 1.1 mmol) ,  
 28 chloromethyl methyl ether (294 mg, 2.3 mmol) and the mixture

1 was stirred at ambient temperature for 12 h. Then the reaction  
 2 mixture was diluted with water (5 mL) and Et<sub>2</sub>O (25 mL) and  
 3 washed with water (10 mL) and brine (10 mL). The organic phase  
 4 was dried over MgSO<sub>4</sub> and concentrated *in vacuo* to a yellow oil.  
 5 Purification by flash column chromatography (silica, 10% EtOAc-  
 6 hexane) followed by reverse phase HPLC separation (partisil 10  
 7 ODS-2, 5% H<sub>2</sub>O-AcCN) afforded the title compound as a pale  
 8 yellow oil.

9 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.24 (s, 3H), 1.29 (t, J = 7.1Hz, 3H), 1.34 (s,  
 10 3H), 1.55-1.60(m, 1H), 1.91-2.05 (m, 3H), 2.24 (s, 3H), 2.38 (s,  
 11 3H), 3.48(s, 3H), 4.16 (q, J = 7.1Hz, 2H), 4.65 (t, J = 4.7Hz, 1H),  
 12 4.76(d, J = 7.0Hz, 1H), 4.87(d, J = 7.0Hz, 1H), 5.80 (s, 1H), 6.33  
 13 (d, J = 15.2Hz, 1H), 6.55 (d, J = 11.5Hz, 1H), 7.01 (dd, J = 11.1,  
 14 15.0Hz, 1H), 7.31 (d, J = 8.3Hz, 1H), 7.37 (dd, J = 2.1, 8.4Hz,  
 15 1H), 7.43 (d, J = 2.1Hz, 1H).

16 (+/-) 7-[4,4-dimethyl-1,2,3,4-tetrahydro-1-(O-methoxymethyl)-  
 17 naphth-7-yl]3,7-dimethyl-hepta-2(E),4(E),6(E)-trienoic acid  
 18 (Compound C27)

19 Employing the same general procedure as for the preparation  
 20 of 7-[4,4-dimethyl-3,4-dihydro-1(2H)-*anti*-(O-ethyl oxime)-naphth-  
 21 7-yl]3,7-dimethyl-hepta-2(E),4(E),6(E)-trienoic acid (Compound  
 22 C25), (-/+ )ethyl 7-[4,4-dimethyl-1,2,3,4-tetrahydro-1-(O-  
 23 methoxymethyl)-naphth-7-yl]3,7-dimethyl-hepta-2(E),4(E),6(E)-  
 24 trienoate (Compound C26, 20 mg, 0.05 mmol) was converted into  
 25 the title compound (white solid).

26 <sup>1</sup>H NMR (acetone-d<sub>6</sub>): δ 1.23 (s, 3H), 1.30 (s, 3H), 1.55-1.60 (m,  
 27 1H), 1.89-1.97 (m, 3H), 2.26 (s, 3H), 2.36 (s, 3H), 3.40 (s, 3H),  
 28 4.59 (t, J = 3.9Hz, 1H), 4.72 (d, J = 6.9Hz, 1H), 4.81 (d, J =

1 7.0Hz, 1H), 5.85 (s, 1H), 6.49 (d, J = 15.1Hz, 1H), 6.66 (d, J =  
 2 11.3Hz, 1H), 7.12 (dd, J = 11.1, 15.1Hz, 1H), 7.36 (d, J = 8.3Hz,  
 3 1H), 7.43 (dd, J = 2.1, 8.3Hz, 1H), 7.49 (d, J = 2.0Hz, 1H).

4 Ethyl 7-[4,4-dimethyl-3,4-dihydro-1-(trimethylsiloxy)-naphth-2-  
 5 yl]3,7-dimethyl-hepta-2(E),4(E),6(E)-trienoate (Compound C28)

6 To a solution of ethyl 7-[4,4-dimethyl-3,4-dihydronaphthalen-  
 7 1(2H)one-7-yl]3,7-dimethyl-hepta-2(E),4(E),6(E)-trienoate  
 8 (Compound C5, 114 mg, 0.33 mmol) in anhydrous THF (10 mL)  
 9 was added sodium bis-(trimethylsilyl) amide (0.36 ml, 0.36 mmol)  
 10 at -78° C under argon. The reaction was stirred at -78 °C for 20  
 11 minutes. To this reaction solution was then added a solution of  
 12 trimethylsilylchloride ( 70.8 mg, 0.65 mmol) in HMPA (0.1 mL)  
 13 and anhydrous THF (5 ml) at -78 °C. The reaction was allowed  
 14 to stir at -78 °C for 2 h. Then the reaction mixture was diluted  
 15 with Et<sub>2</sub>O (25 mL) and washed with water (10 mL), brine (10  
 16 mL). The organic phase was dried over MgSO<sub>4</sub> and  
 17 concentrated *in vacuo* to a yellow oil. The product was purified  
 18 by flash column chromatography (silica, 10% EtOAc-hexane) to  
 19 afford the title compound as a pale yellow oil.

20 <sup>1</sup>H NMR (acetone-d<sub>6</sub>): δ 0.26 (s, 9H), 1.23 (t, J = 7.1Hz, 3H),  
 21 1.26 (s, 6H), 2.25 (m, 5H), 2.37 (m, 3H), 4.08 (q, J = 7.1Hz, 2H),  
 22 5.15 (t, J = 4.6Hz, 1H), 5.83 (s, 1H), 6.48 (d, J = 15.1Hz, 1H),  
 23 6.65 (d, J = 11.0Hz, 1H), 7.13 (dd, J = 11.1, 15.0Hz, 1H), 7.26 (d,  
 24 J = 8.1Hz, 1H), 7.40 (dd, J = 2.1, 8.1Hz, 1H), 7.60 (d, J = 2.1Hz,  
 25 1H).

26 (+/-)Ethyl 7-[4,4-dimethyl-1,2,3,4-tetrahydro-1(RS)-(2'(RS)-  
 27 tetrahydropyranoxy)-3,7-dimethyl--naphth-2-yl]hepta-  
 28 2(E),4(E),6(E)-trienoate (Compound C29a)

1 (+/-)Ethyl 7-[4,4-dimethyl-1,2,3,4-tetrahydro-1(RS)-(2'(SR))-  
 2 tetrahydropyranoxy)-3,7-dimethyl--naphth-2-yl]hepta-  
 3 2(E),4(E),6(E)-trienoate (Compound C29b)

4 To a solution of (-/+ )ethyl 7-[4,4-dimethyl-1,2,3,4-tetrahydro-  
 5 1-hydroxy -naphth-7-yl]3,7-dimethyl-hepta-2(E),4(E),6(E)-trienoate  
 6 (Compound C13, 110 mg, 0.3 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (2 mL)  
 7 was added 3,4-dihydro-2H-pyran (62 mg, 0.7 mmol) followed by  
 8 pyridinium p-toluenesulfonate (10 mg, 0.04 mmol). The reaction  
 9 mixture was stirred at ambient temperature for 24 h. The  
 10 reaction mixture was diluted with Et<sub>2</sub>O (20 mL) and washed  
 11 successively with saturated NaHCO<sub>3</sub> (10 mL) ,water (10 mL) and  
 12 brine (10 mL). The organic phase was dried over MgSO<sub>4</sub> and  
 13 concentrated *in vacuo* to a yellow oil. Purification by flash  
 14 column chromatography (silica, 15% EtOAc-hexane) followed by  
 15 reverse phase HPLC separation (partisil 10 ODS-2, 5% H<sub>2</sub>O-  
 16 AcCN) afforded the title compounds as pale yellow oils .  
 17 (+/-)Ethyl 7-[4,4-dimethyl-1,2,3,4-tetrahydro-1(RS)-(2'(RS))-  
 18 tetrahydropyranoxy)-3,7-dimethyl--naphth-2-yl]hepta-  
 19 2(E),4(E),6(E)-trienoate (Compound C29a)  
 20 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.25-1.31 (m, 9H), 1.52-2.03 (m, 10H), 2.24  
 21 (s, 3H), 2.38 (s, 3H), 3.50-3.60 (m, 1H), 4.01-4.07 (m, 1H), 4.12 (q,  
 22 J = 7.1Hz, 2H), 4.77 (t, J = 4.5Hz, 1H), 4.94 (t, J = 3.5Hz, 1H),  
 23 5.80 (s, 1H), 6.32 (d, J = 15.0Hz, 1H), 6.56 (d, J = 11.5Hz, 1H),  
 24 7.02 (dd, J = 11.1, 15.0Hz, 1H), 7.28 (d, J = 8.3Hz, 1H), 7.36 (dd,  
 25 J = 2.1, 8.3Hz, 1H), 7.62 (d, J = 2.0Hz, 1H).  
 26 (+/-)Ethyl 7-[4,4-dimethyl-1,2,3,4-tetrahydro-1(RS)-(2'(SR))-  
 27 tetrahydropyranoxy)-3,7-dimethyl--naphth-2-yl]hepta-  
 28 2(E),4(E),6(E)-trienoate (Compound C29b)

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.25-1.32 (m, 9H), 1.52-2.08 (m, 10H), 2.45  
 (s, 3H), 2.38 (s, 3H), 3.54-3.61 (m, 1H), 3.97-4.03 (m, 1H), 4.14 (q,  
 J = 7.1Hz, 2H), 4.68 (t, J = 5.0Hz, 1H), 4.87 (t, J = 4.4Hz, 1H),  
 5.81 (s, 1H), 6.34 (d, J = 15.2Hz, 1H), 6.54 (d, J = 11.0Hz, 1H),  
 7.01 (dd, J = 11.2, 15.1Hz, 1H), 7.30-7.40 (m, 3H)  
(+/-)7-[4,4-Dimethyl-1,2,3,4-tetrahydro-1(RS)-(2'(RS)-  
tetrahydropyranoxy)-3,7-dimethyl--naphth-2-yl]hepta-  
2(E),4(E),6(E)-trienoic acid (Compound C31)

Employing the same general procedure as for the preparation  
 of 7-[4,4-dimethyl-3,4-dihydro-1(2H)-*anti*-(O-ethyl oxime)-naphth-  
 7-yl]3,7-dimethyl-hepta-2(E),4(E),6(E)-trienoic acid (Compound  
 C25), (+/-)ethyl 7-[4,4-dimethyl-1,2,3,4-tetrahydro-1(RS)-(2'(RS)-  
 tetrahydropyranoxy)-3,7-dimethyl--naphth-2-yl]hepta-  
 2(E),4(E),6(E)-trienoate (Compound C29a, 15 mg, 0.03 mmol)  
 was converted into the title compound (white solid).

<sup>1</sup>H NMR (acetone-d<sub>6</sub>): δ 1.24 (s, 3H) 1.29 (s, 3H), 1.52-2.03 (m,  
 10H), 2.26 (s, 3H), 2.37 (s, 3H), 3.56-3.61 (m, 1H), 3.99-4.03 (m,  
 1H), 4.70 (t, J = 4.5Hz, 1H), 4.91 (t, J = 3.7Hz, 1H), 5.80 (s,  
 1H), 6.49 (d, J = 15.0Hz, 1H), 6.66 (d, J = 11.3Hz, 1H), 7.13  
 (dd, J = 11.1, 15.0Hz, 1H), 7.34 (d, J = 8.3Hz, 1H), 7.42 (dd, J =  
 2.1, 8.3Hz, 1H), 7.63 (d, J = 2.0Hz, 1H).

7-Acetyl-1(2H)-(propyliden-2-yl)-3,4-dihydro-4,4-  
dimethylnaphthalene (Compound C33)

To a solution of 7-bromo-1(2H)-(propyliden-2-yl)-3,4-dihydro-  
 4,4-dimethylnaphthalene (Compound A37, 698 mg, 2.5 mmol) in  
 anhydrous THF (15 mL) was added (1-ethoxyvinyl)tributyltin (1.8  
 g, 5 mmol) and bis(triphenylphosphine)palladium(II) chloride (20  
 mg). The resultant mixture was refluxed under argon atmosphere



for 24 h. The reaction mixture was cooled to ambient temperature and quenched with 10% HCl(5 mL), stirred for 20 minutes and extracted with Et<sub>2</sub>O (3 x 20 mL). The organic layer was washed with water (10 mL), saturated NaHCO<sub>3</sub> (10 mL), brine (10 mL) and dried over MgSO<sub>4</sub>. The crude material was purified by flash column chromatography (silica, 5% EtOAc-hexane) to afford the title compound as a colorless oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.25 (s, 6H), 1.60 (t, J = 6.9Hz, 2H), 1.84 (s, 3H), 1.97 (s, 3H), 2.49 (t, J = 6.9Hz, 2H), 2.57 (s, 3H), 7.35 (d, J = 8.3Hz, 1H), 7.73 (dd, J = 2.0, 8.2Hz, 1H), 7.85 (d, J = 1.9Hz, 1H).

3-[1(2H)-(Propyliden-2-yl))-3,4-dihydro-4,4-dimethylnaphthalen-7-yl]but-2(E)-en-nitrile (Compound C34)

To a slurry of NaH (117 mg, 4.8 mmol) in anhydrous THF (10 mL) was added a solution of ethylcyanomethylphosphonate (947 mg, 5.4 mmol) in THF (2 mL) at -78 °C under argon atmosphere. The reaction was allowed to warm to ambient temperature and a solution of 7-acetyl-1(2H)-(propyliden-2-yl)-3,4-dihydro-4,4-dimethylnaphthalene (Compound C33, 394 mg, 1.6 mmol) in 5 mL of THF was added dropwise. The resultant reaction was stirred for 16 h at ambient temperature and quenched with water (5 mL). After extraction with EtOAc (2 x 10 mL), the combined organic layer was dried over MgSO<sub>4</sub>, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, 5% EtOAc-hexane) to afford the title compound as a colorless oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.24 (s, 6H), 1.60 (t, J = 7.0Hz, 2H), 1.85 (s, 3H), 1.96 (s, 3H), 2.45 (s, 3H), 2.49 (t, J = 6.8Hz, 2H), 5.59 (s,

1 1H), 7.24-7.35 (m, 3H). 3-[1(2H)-(Propyliden-2-yl)-3,4-dihydro-4,4-  
 2 dimethylnaphthalen-7-yl]but-2(E)-en-aldehyde (Compound C35)

3 To a solution of 3-[1(2H)-(propyliden-2-yl)-3,4-dihydro-4,4-  
 4 dimethylnaphthalen-7-yl]but-2(E)-en-onitrile (Compound C34,  
 5 311 mg, 1.2 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (10 ml) was added a  
 6 solution of diisobutylaluminum hydride (1M in  $\text{CH}_2\text{Cl}_2$ ) (2.8 ml,  
 7 2.8 mmol) dropwise at  $-78^\circ\text{C}$ , under argon atmosphere. The  
 8 reaction was allowed to stir at  $-78^\circ\text{C}$  for 6 h. A mixture of  $\text{H}_2\text{O}$   
 9 (10 ml) and  $\text{CH}_2\text{Cl}_2$  (10 ml) was added and the resultant gel was  
 10 filtered. The filtrate was concentrated *in vacuo* to a yellow oil.

11 Purification by flash column chromatography (silica, 10% EtOAc-  
 12 hexane) afforded the title compound as a pale yellow oil.

13  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.26 (s, 6H), 1.62 (t,  $J = 7.0\text{Hz}$ , 2H), 1.86 (s,  
 14 3H), 1.98 (s, 3H), 2.50 (t,  $J = 6.9\text{Hz}$ , 2H), 2.57 (s, 3H), 6.40 (d,  $J$   
 15  $= 9.3\text{Hz}$ , 1H), 7.35-7.39 (m, 2H), 7.45 (d,  $J = 1.9\text{Hz}$ , 1H), 10.17  
 16 (d,  $J = 7.9\text{Hz}$ , 1H).

17 Ethyl-7-[1(2H)-(propyliden-2-yl)-3,4-dihydro-4,4-dimethyl-  
 18 naphthalen-7-yl]-3,7-dimethyl-hept-2(E),4(E),6(E)-trienoate  
 19 (Compound C36)

20 Employing the same general procedure as for the preparation  
 21 of ethyl 7-[4,4-dimethyl-3,4-dihydronaphthalen-1(2H)one-7-yl]3,7-  
 22 dimethyl-hepta-2(E),4(E),6(E)-trienoate (Compound C5), 3-  
 23 [1(2H)-(propyliden-2-yl)-3,4-dihydro-4,4-dimethylnaphthalen-7-  
 24 yl]but-2(E)-en-aldehyde (Compound C35, 178 mg, 0.6 mmol) was  
 25 converted into the title compound (pale yellow thick syrup).

26  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.24 (s, 6H), 1.27 (t,  $J = 7.0\text{Hz}$ , 3H), 1.60 (t,  
 27  $J = 6.9\text{Hz}$ , 2H), 1.84 (s, 3H), 1.98 (s, 3H), 2.24 (s, 3H), 2.37 (s,  
 28 3H), 2.48 (t,  $J = 6.7\text{Hz}$ , 2H), 4.14 (q,  $J = 7.1\text{Hz}$ , 2H), 5.79 (s,

1 1H), 6.33 (d, J = 14.9Hz, 1H), 6.54 (d, J = 10.9Hz, 1H), 6.98 (dd,  
2 J = 11.0, 15.0Hz, 1H), 7.25-7.28 (m, 2H), 7.36 (s, 1H).

3  
4 7-Bromo-1(2H)-(phenylbenzyliden-yl)-3,4-dihydro-4,4-  
5 dimethylnaphthalene (Compound C37)

6 Employing the same general procedure as for the preparation  
7 of 7-bromo-1(2H)-(propyliden-2-yl)-3,4-dihydro-4,4-  
8 dimethylnaphthalene (Compound A37), 7-bromo-3,4-dihydro-4,4-  
9 dimethylnaphthalen-1(2H)-one (Compound G, 1.0 g, 3.96 mmol)  
10 was converted into the title compound (white solid) using titanium  
11 trichloride (5 g, 32 mmol), lithium wire (0.7 g, 100 mmol) and  
12 benzophenone (800 mg, 4.4 mmol).

13 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.31 (s, 6H), 1.66 (t, J = 6.6Hz, 2H), 2.52 (t,  
14 J = 6.8Hz, 2H), 6.92 (d, J = 1.7Hz, 1H), 6.98-7.00 (m, 2H), 7.15-  
15 7.21 (m, 6H), 7.25-7.36 (m, 4H).

16 7-Acetyl-1(2H)-(phenylbenzyliden-yl)-3,4-dihydro-4,4-  
17 dimethylnaphthalene (Compound C38)

18 Employing the same general procedure as for the preparation  
19 of 7-acetyl-1(2H)-(propyliden-2-yl)-3,4-dihydro-4,4-  
20 dimethylnaphthalene (Compound C33), 7-bromo-1(2H)-  
21 (phenylbenzyliden-yl)-3,4-dihydro-4,4-dimethylnaphthalene  
22 (Compound C37, 255 mg, 0.63 mmol) was converted into the title  
23 compound (colorless oil) using (1-ethoxyvinyl)tributyltin (353 mg,  
24 0.97 mmol) and bis(triphenylphosphine)palladium(II) chloride (20  
25 mg).

26 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.34 (s, 6H), 1.70 (t, J = 6.4Hz, 2H), 1.99 (s,  
27 3H), 2.57 (t, J = 6.7Hz, 2H), 7.01-7.04 (m, 2H), 7.12-7.45 (m,  
28 10H), 7.65 (dd, J = 1.9, 8.3Hz, 1H).

1 3-(1(2H)-(phenylbenzylidenyl)-3,4-dihydro-4,4-dimethylnaphth-7-  
 2 yl)-but-2(E)-enonitrile (Compound C39)

3 Employing the same general procedure as for the preparation  
 4 of 3-(1(2H)-(propyliden-2-yl)-3,4-dihydro-4,4-  
 5 dimethylnaphthyl)but-2(E)-enonitrile (Compound C34), the 7-  
 6 acetyl-1(2H)-(phenylbenzylidenyl)-3,4-dihydro-4,4-  
 7 dimethylnaphthalene (Compound 38, 206 mg, 0.56 mmol) was  
 8 converted into the title compound (colorless oil) using 327 mg  
 9 (1.85 mmol) of ethylcyanomethylphosphonate and 40.3 mg (1.68  
 10 mmol) of sodium hydride.

11 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.34 (s, 6H), 1.70 (t, J = 6.3Hz, 2H), 2.03 (s,  
 12 3H), 2.57 (t, J = 6.8Hz, 2H), 4.88 (s, 1H), 7.01 (dd, J = 2.0,  
 13 7.3Hz, 2H), 7.14-7.37 (m, 11H).

14 3-(1(2H)-(phenylbenzylidenyl)-3,4-dihydro-4,4-dimethylnaphth-7-  
 15 yl)-but-2(E)-enaldehyde (Compound C40)

16 Employing the same general procedure as for the preparation  
 17 of 3-(1(2H)-(propyliden-2-yl)-3,4-dihydro-4,4-dimethylnaphthyl)-  
 18 but-2(E)-enaldehyde (Compound C35), 3-(1(2H)-  
 19 (phenylbenzylidenyl)-3,4-dihydro-4,4-dimethylnaphth-7-yl)-but-2-  
 20 enonitrile (Compound C39, 156 mg, 0.40 mmol) was converted  
 21 into the title compound (pale yellow solid) using 0.9 ml (0.88  
 22 mmol) of diisobutylaluminum hydride (1M in CH<sub>2</sub>Cl<sub>2</sub>).

23 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.35 (s, 6H), 1.70 (t, J = 6.5Hz, 2H), 2.04 (s,  
 24 3H), 2.57 (t, J = 6.7Hz, 2H), 5.88 (d, J = 7.7Hz, 1H), 7.02 (dd, J  
 25 = 1.5, 7.4Hz, 2H), 7.12-7.36 (m, 11H), 9.98 (d, J = 7.8Hz, 1H).

26 Ethyl 7-[4,4-dimethyl-3,4-dihydro-1(2H)-(phenylbenzylidenyl)-  
 27 naphth-7-yl]-3,7-dimethyl-hepta-2(E),4(E),6(E)-trienoate  
 28 (Compound C41)

1       Employing the same general procedure as for the preparation  
2 of ethyl 7-[4,4-dimethyl-3,4-dihydronaphthalen-1(2H)one-7-yl]3,7-  
3 dimethyl-hepta-2(E),4(E),6(E)-trienoate (Compound C5), 3-  
4 (1(2H)-(phenylbenzylidenyl)-3,4-dihydro-4,4-dimethylnaphth-7-yl)-  
5 but-2(E)-enaldehyde (Compound C40, 101 mg, 0.26 mmol) was  
6 converted into the title compound (pale yellow thick oil).  
7  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.28 (t,  $J = 7.1\text{Hz}$ , 3H), 1.34 (s, 6H), 1.69 (t,  
8  $J = 6.3\text{Hz}$ , 2H), 1.85 (s, 3H), 2.32 (s, 3H), 2.54 (t,  $J = 6.9\text{Hz}$ , 2H),  
9 4.14 (q,  $J = 7.1\text{Hz}$ , 2H), 5.74 (d,  $J = 8.7\text{Hz}$ , 1H), 5.77 (s, 1H),  
10 6.15 (d,  $J = 14.9\text{Hz}$ , 1H), 6.80 (dd,  $J = 11.2, 15.0\text{Hz}$ , 1H), 7.04-  
11 7.36 (m, 13H).

12 7-Bromo-1-(1,1-dimethylethyl)-3,4-dihydro-4,4-  
13 dimethylnaphthalene (Compound C42)

14       In a flame dried round bottom flask 7-bromo-3,4-dihydro-4,4-  
15 dimethylnaphthalen-1(2H)-one (Compound G, 2.0 g, 7.93 mmol)  
16 was dissolved in anhydrous THF (50 ml) and 3,4,5,6,-tetrahydro-  
17 2(H)-pyrimidinone (DMPU) (11.5 ml, 95.16 mmol) was added,  
18 under argon atmosphere. The reaction was then cooled to  $-20^\circ\text{C}$   
19 and a solution of t-butyl magnesium chloride (16 ml, 31.7 mmol)  
20 (2 M in  $\text{Et}_2\text{O}$ ) was added dropwise and stirred at  $-20^\circ\text{C}$  for 2 h  
21 and at ambient temperature for 1 h, under argon atmosphere.  
22 The reaction was quenched at  $0^\circ\text{C}$  with saturated ammonium  
23 chloride solution (20 ml) and extracted with EtOAc (2 x 50 ml).  
24 The combined extract was washed with water (20 ml), brine (20  
25 ml) and dried over  $\text{MgSO}_4$ . The solvent was evaporated under  
26 reduced pressure to afford a yellow oil. To this yellow oil were  
27 added MeOH (50 ml) and p-tolylsulfonic acid (100 mg). The  
28 resultant reaction solution was heated in an oil bath ( $60^\circ\text{C}$ ) for 3

h. The reaction was cooled and quenched with water (20 ml), extracted with EtOAc (2 x 50 ml). The combined extract was washed with saturated NaHCO<sub>3</sub> (20 ml), water (20 ml), brine (20 ml), and dried over MgSO<sub>4</sub>. The solvent was concentrated *in vacuo* and the title compound was obtained as a colorless oil after purification by flash chromatography (silica, hexane).  
<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.17 (s, 6H), 1.32 (s, 9H), 2.10 (d, J = 5.0Hz, 2H), 5.95 (t, J = 4.9Hz, 1H), 7.13 (d, J = 8.3Hz, 1H), 7.24 (dd, J = 2.1, 8.3Hz, 1H), 7.74 (d, J = 2.0Hz, 1H).

7-Acetyl-1-(1,1-dimethylethyl)-3,4-dihydro-4,4-dimethylnaphthalene (Compound C43)

Employing the same general procedure as for the preparation of 7-acetyl-1(2H)-(propyliden-2-yl)-3,4-dihydro-4,4-dimethylnaphthalene (Compound C33), 7-bromo-1-(1,1-dimethylethyl)-3,4-dihydro-4,4-dimethylnaphthalene (Compound C42, 539 mg, 1.84 mmol) was converted into the title compound (white solid), using (1-ethoxyvinyl)tributyltin (2.6 g, 7.36 mmol) and bis(triphenylphosphine)palladium(II) chloride (80 mg).

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.25 (s, 6H), 1.39 (s, 9H), 2.16 (d, J = 4.9Hz, 2H), 2.60 (s, 3H), 6.00 (t, J = 4.9Hz, 1H), 7.39 (d, J = 8.1Hz, 1H), 7.75 (dd, J = 1.7, 8.0Hz, 1H), 8.29 (d, J = 1.8Hz, 1H).

3-[1-(1,1-dimethylethyl)-3,4-dihydro-4,4-dimethyl-naphthyl]-2-but-2(E)-enonitrile (Compound C44)

Employing the same general procedure as for the preparation of 3-(1-propylidene)-1,2,3,4-tetrahydro-4,4-dimethylnaphthyl)but-2(E)-enonitrile (Compound C34), 7-acetyl-1-(1,1-dimethylethyl)-3,4-dihydro-4,4-dimethylnaphthalene (Compound C43, 326 mg,

1 1.26 mmol) was converted into the title compound (white solid)  
 2 using 742 mg (4.19 mmol) of ethylcyanomethylphosphonate and 91  
 3 mg (3.80 mmol) of sodium hydride.

4  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.22 (s, 6H), 1.36 (s, 9H), 2.14 (d, J =  
 5 4.9Hz, 2H), 2.47 (s, 3H), 5.58 (s, 1H), 6.00 (t, J = 4.9Hz, 1H),  
 6 7.26 (dd, J = 2.0, 8.2Hz, 1H), 7.32 (d, J = 8.1Hz, 1H), 7.73 (d, J  
 7 = 1.9Hz, 1H).

8 3-[1-(1,1-dimethylethyl)-3,4-dihydro-4,4-dimethyl-naphth-7-yl]-but-  
 9 2(E)-enaldehyde (Compound C45)

10 Employing the same general procedure as for the preparation  
 11 of 3-(1-propylidene)-1,2,3,4-tetrahydro-4,4-dimethylnaphthyl)-but-  
 12 2(E)-enaldehyde (Compound C35), (E)- 3-(1-(1,1-dimethylethyl)-  
 13 3,4-dihydro-4,4-dimethylnaphthyl)-but-2(E)-enonitrile (Compound  
 14 C45, 256 mg, 0.95 mmol) was converted into the title compound  
 15 (pale yellow solid) using 2.8 ml (2.84 mmol) of  
 16 diisobutylaluminum hydride (1M in  $\text{CH}_2\text{Cl}_2$ ).

17  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.25 (s, 6H), 1.30 (s, 9H), 2.16 (d, J =  
 18 5.0Hz, 2H), 2.60 (s, 3H), 6.01 (t, J = 4.9Hz, 1H), 6.41 (d, J =  
 19 7.8Hz, 1H), 7.38 (m, 2H), 7.86 (s, 1H), 10.19 (d, J = 8.0Hz, 1H).

20 Ethyl 7-[4,4-dimethyl-3,4-dihydro-1-(1,1-dimethylethyl)-naphth-7-  
 21 yl]-3,7-dimethyl-hepta-2(E),4(E),6(E)-trienoate (Compound C46)

22 Employing the same general procedure as for the preparation  
 23 of ethyl 3,7-dimethyl-7-[5,5-dimethyl-5,6,7,8-tetrahydro-8-oxo-  
 24 naphth-2-yl]hepta-2(E),4(E),6(E)-trienoate (Compound C5, (E)- 3-  
 25 [1-(1,1-dimethylethyl)-3,4-dihydro-4,4-dimethyl-naphthyl]-2-butene-  
 26 1-aldehyde (Compound C45, 82.6 mg, 0.29 mmol) was converted  
 27 into the title compound (pale yellow solid).

28  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.24 (s, 6H), 1.28 (t, J = 7.1Hz, 3H), 1.39 (s,

9H), 2.15 (d, J = 4.9Hz, 2H), 2.28 (s, 3H), 2.40 (s, 3H), 4.15 (q, J = 7.1Hz, 2H), 5.83 (s, 1H), 5.97 (t, J = 4.9Hz, 1H), 6.36 (d, J = 15.2Hz, 1H), 6.54 (d, J = 11.5Hz, 1H), 7.00 (dd, J = 11.1, 15.0Hz, 1H), 7.31 (s, 2H), 7.78 (s, 1H).

(+/-) Ethyl 4-[(5,5-dimethyl-8-hydroxy-8-carbethoxymethyl-5,6,7,8-tetrahydronaphth-2-yl)azo]benzoate (Compound D1)

To a refluxing solution of zinc dust (0.15 g, 20 mesh, activated prior to use by washing with 2% of hydrochloric acid, water, 95% ethanol, acetone and anhydrous ether, then dried in vacuum for several hours) in 6 ml of dry benzene was slowly added a mixture of bromo ethyl acetate (0.082 ml, 0.74 mmol) and ethyl 4-[(5,5-dimethyl-5,6-dihydro-naphthalen-8(7H)-one-2-yl)azo]benzoate (Compound D10, 0.13 g, 0.371 mmol) in 6 ml of dry benzene. The resulting mixture was refluxed for 2 h then cooled to room temperature. The precipitate was filtered through celite and the filtrate was washed with cold 15% sulfuric acid. The organic phase was washed with saturated sodium bicarbonate, brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give a red oil. Purification by flash chromatography (silica gel, 30% ethyl acetate in hexane) afforded the title compound as a red oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.28 (t, J = 7.14 Hz, 3H), 1.34 (3H, s), 1.37 (s, 3H), 1.43 (t, J = 7.14 Hz, 3H), 1.81 (m, 2H), 2.12 (m, 2H), 2.90 (q, J = 7.14 Hz, 2H), 4.22 (q, J = 7.14 Hz, 2H), 4.42 (q, J = 7.14 Hz, 2H), 7.46 (d, J = 8.43 Hz, 1H), 7.80 (dd, J = 2.07, 6.35 Hz, 1H), 7.91 (d, J = 8.55 Hz, 2H), 8.17 (d, J = 8.55 Hz, 2H), 8.20 (d, J = 2.20 Hz, 1H).

Ethyl 4-[(5,5-dimethyl-8(7H)-(carbethoxymethylideneyl)-5,6-dihydronaphthalen-2-yl)azo]benzoate (Compound D2a)



1 Ethyl 4-[(5,5-dimethyl-8-(carbethoxymethyl)-5,6-  
 2 dihydronaphthalen-2-yl)azo]benzoate (Compound D2b)

3 A solution of (+/-) ethyl 4-[(5,5-dimethyl-8-hydroxy-8-  
 4 carbethoxymethyl-5,6,7,8-tetrahydronaphth-2-yl)azo]benzoate  
 5 (Compound D1, 108 mg, 0.25 mmol), DCC (55.9 mg, 0.271 mmol)  
 6 and CuCl (36.6 mg, 0.37 mmol) in 8 ml of dry benzene was heated  
 7 under reflux for 7 days. After cooling to room temperature, the  
 8 solids were filtered out and the solution was extracted with ethyl  
 9 acetate. The combined organic layer was washed with brine and  
 10 dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under reduced  
 11 pressure, the crude material was purified by flash chromatography  
 12 (silicagel, 10 % ethyl acetate in hexane) to afford the pure title  
 13 compounds as red oils.

14 Ethyl 4-[(5,5-dimethyl-8(7H)-(carbethoxymethylidenyl)-5,6-  
 15 dihydronaphthalen-2-yl)azo]benzoate (Compound D2a)

16 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.35 (m, 9H), 1.44 (t, J = 7.14 Hz, 3H), 1.79  
 17 (t, J = 6.75 Hz, 2H), 3.29 (t, J = 6.59 Hz, 2H), 4.27 (q, J = 7.14  
 18 Hz, 2H), 4.44 (q, J = 7.14 Hz, 2H), 6.47 (s, 1H), 7.55 (d, J = 8.42  
 19 Hz, 1H), 7.97 (m, 3H), 8.22 (m, 3H).

20 Ethyl 4-[(5,5-dimethyl-8-(carbethoxymethyl)-5,6-  
 21 dihydronaphthalen-2-yl)azo]benzoate (Compound D2b)

22 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.22 (t, J = 7.10 Hz, 3H), 1.35 (s, 6H), 1.44  
 23 (t, J = 7.14 Hz, 3H), 2.32 (d, J = 4.39 Hz, 2H), 3.56 (s 2H), 4.17  
 24 (q, J = 7.14 Hz, 2H), 4.44 (q, J = 7.14 Hz, 2H), 6.20 (t, J = 4.45  
 25 Hz, 1H), 7.48 (d, J = 8.80 Hz, 1H), 7.81 (m, 2H), 7.92 (d, J =  
 26 8.49 Hz, 2H), 8.20 (d, J = 8.48 Hz, 2H).

27 Ethyl 4-[(8(7H)-anti-(O-methyl oxime)-5,5-dimethyl-5,6-  
 28 dihydronaphthalen-2-yl)azo]benzoate (Compound D3)

1 A solution of ethyl 4-[(5,5-dimethyl-5,6-dihydro-naphthalen-  
 2 8(7H)-one-2-yl)azo]benzoate (Compound D10, 0.13 g, 0.371  
 3 mmol) (40mg, 0.114 mmol), NaOAc (29.3 mg, 0.286 mmol) and  
 4 methoxy amine hydrochloride (14.3 mg, 0.137 mmol) in 3 ml of  
 5 EtOH and 2 ml of THF was stirred at room temperature for two  
 6 weeks. The solvent was distilled off and the residue was diluted  
 7 with ethyl acetate. The solution was washed with NaHCO<sub>3</sub> (sat.),  
 8 water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed  
 9 under reduced pressure, the residue was purified by flash  
 10 chromatography to afford the title compound as a red solid (34.8  
 11 mg).

12 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.35 (s, 3H), 1.44 (t, J = 7.14 Hz, 3H), 1.78  
 13 (t, J = 6.96 Hz, 2H), 2.83 (t, J = 6.90 Hz, 2H), 4.06 (s, 3H), 4.43  
 14 (q, J = 7.14 Hz, 2H), 7.51 (d, J = 8.48 Hz, 1H), 7.82 (dd, J =  
 15 2.20, 6.35 Hz, 1H), 7.96 (d, J = 8.55 Hz, 2H), 8.21 (d, J = 8.48  
 16 Hz, 2H), 8.56 (d, J = 2.14 Hz, 1H).

17 4-[(8(7H)-Anti-(O-methyl oxime)-5,5-dimethyl-5,6-  
 18 dihydronaphthalen-2-yl)azo]benzoic acid (Compound D4)

19 A solution of ethyl 4-[(8(7H)-anti-(O-methyl oxime)-5,5-  
 20 dimethyl-5,6-dihydronaphthalen-2-yl)azo]benzoate (Compound  
 21 D3, 57.7 mg, 0.16 mmol) and 2 ml of aqueous NaOH (12%) in 4  
 22 ml of THF and 2 ml of EtOH was stirred overnight at room  
 23 temperature. The reaction was acidified with 10% HCl (to pH 4  
 24 and extracted with EtOAc. The combined organic layer was  
 25 washed with water and brine, and dried over Na<sub>2</sub>SO<sub>4</sub>. Solvent was  
 26 removed under reduced pressure to afford the title compound as a  
 27 red solid.

28 <sup>1</sup>H NMR (acetone-d<sub>6</sub>): δ 1.35 (s, 3H), 1.78 (t, J = 6.96 Hz, 2H),

1 2.82 (t,  $J = 6.90$  Hz, 2H), 4.00 (s, 3H), 7.67 (d,  $J = 8.54$  Hz, 1H),  
 2 7.90 (dd,  $J = 2.20, 6.59$  Hz, 1H), 8.03 (d,  $J = 8.66$  Hz, 2H), 8.24  
 3 (d,  $J = 8.48$  Hz, 2H), 8.54 (d,  $J = 2.14$  Hz, 1H).

4 (+/-) Ethyl 4-[(5,5-dimethyl-8-hydroxy-5,6,7,8-  
 5 tetrahydronaphthalen-2-yl)azo]benzoate (Compound D5)

6 To a solution of ethyl 4-[(5,5-dimethyl-5,6-dihydro-  
 7 naphthalen-8(7H)-one-2-yl)azo]benzoate (Compound D10, 60  
 8 mg, 0.171 mmol) in 2 ml of THF and 7 ml of EtOH at 0 °C was  
 9 added  $\text{NaBH}_4$  (6.5 mg, 0.171 mmol) and the mixture stirred for 3  
 10 h. The reaction was quenched by slow addition of cold water.  
 11 Solvent was removed under reduced pressure and the residue was  
 12 extracted with ethyl acetate. The organic layer was washed with  
 13 brine, dried ( $\text{MgSO}_4$ ) and solvent removed under reduced  
 14 pressure. The crude product was purified by flash chromatography  
 15 (silica, ethyl acetate/hexane, 1 : 3) to afford the title compound as  
 16 a red oil.

17  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.31 (s, 3H), 1.38 (s, 3H), 1.43 (t,  $J = 7.14$   
 18 Hz, 3H), 1.68 (m, 1H), 1.92 (m, 2H), 2.13 (m, 1H), 4.42 (q,  $J =$   
 19 7.14 Hz, 2H), 4.85 (m, 1H), 7.49 (d,  $J = 8.48$  Hz, 1H), 7.85 (dd,  $J$   
 20 = 2.2, 6.29 Hz, 1H), 7.94 (d,  $J = 8.61$  Hz, 2H), 8.05 (d,  $J = 2.13$   
 21 Hz, 1H), 8.20 (d,  $J = 8.55$  Hz, 2H).

22 (+/-) Ethyl 4-[(5,5-dimethyl-8-(methoxymethoxy)-5,6,7,8-  
 23 tetrahydronaphthalen-2-yl)azo]benzoate (Compound D6)

24 To a solution of (+/-) ethyl 4-[(5,5-dimethyl-8-hydroxy-  
 25 5,6,7,8-tetrahydronaphthalen-2-yl)azo]benzoate (Compound D5,  
 26 49.7 mg, 0.141 mmol) in 4 ml of dry  $\text{CH}_2\text{Cl}_2$  at 0 °C was added  
 27 isopropyl ethyl amine (0.152 ml, 0.847 mmol) followed by  
 28 chloromethyl methyl ether (0.0323 ml, 0.423 mmol). The reaction

1 mixture was stirred at room temperature for 12 h. Solvent was  
 2 removed under reduced pressure, the residue was dissolved in  
 3 ethyl acetate and the solution was washed with  $\text{NaHCO}_3$  (sat.),  
 4 and brine. The organic layer was dried ( $\text{MgSO}_4$ ). The solvent  
 5 was removed under reduced pressure, the residue was purified by  
 6 flash chromatography (silica, ethyl acetate : hexane, 1 : 3) to  
 7 afford the title compound as a red oil.

8  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.31 (s, 3H), 1.39 (s, 3H), 1.43 (t,  $J$  = 7.08  
 9 Hz, 3H), 1.64 (m, 1H), 2.07 (m, 3H), 3.52 (s, 3H), 4.43 (q,  $J$  =  
 10 7.08 Hz, 2H), 4.75 (t,  $J$  = 5.06 Hz, 1H), 4.84 (d,  $J$  = 6.90 Hz, 1H),  
 11 4.93 (d,  $J$  = 6.90 Hz, 1H), 7.50 (d,  $J$  = 8.43 Hz, 1H), 7.83 (dd,  $J$   
 12 = 2.19, 6.29 Hz, 1H), 7.95 (m, 3H), 8.19 (d,  $J$  = 8.55 Hz, 2H).

13 (+/-) 4-[(5,5-Dimethyl-8-(methoxymethoxy)-5,6,7,8-  
 14 tetrahydronaphthalen-2-yl)azo]benzoic acid (Compound D7)

15 Using the same procedure as for the preparation of 4-  
 16 [(8(7H)-anti-(O-methyl oxime)-5,5-dimethyl-5,6-  
 17 dihydronaphthalen-2-yl)azo]benzoic acid (Compound D4), (+/-)  
 18 ethyl 4-[(5,5-dimethyl-8-(methoxymethoxy)-5,6,7,8-  
 19 tetrahydronaphthalen-2-yl)azo]benzoate (Compound D6, 34 mg,  
 20 0.093 mmol) was converted into the title compound (red solid).  
 21  $^1\text{H}$  NMR (acetone- $d_6$ ):  $\delta$  1.32 (s, 3H), 1.37 (s, 3H), 1.63 (m, 1H),  
 22 1.99 (m, 3H), 3.45 (s, 3H), 4.75 (t,  $J$  = 6.1 Hz, 1H), 4.80 (d,  $J$  =  
 23 6.96 Hz, 1H), 4.89 (d,  $J$  = 6.96 Hz, 1H), 7.62 (d,  $J$  = 8.55 Hz,  
 24 1H), 7.84 (dd,  $J$  = 2.19, 6.29 Hz, 1H), 8.00 (m, 3H), 8.22 (d,  $J$  =  
 25 8.55 Hz, 2H).

26 3,4-dihydro-4,4-dimethyl-7-nitro-naphthalen-1(2H)-one  
 27 (Compound D8)

28 To 1.7 mL (3.0g, 30.6 mmol, 18M)  $\text{H}_2\text{SO}_4$  at  $-5^\circ\text{C}$  (ice-NaCl

1 bath) was slowly added 783.0 mg (4.49 mmol) of 3,4-dihydro-4,4-  
 2 dimethyl-naphthalen-1(2H)-one. A solution of HNO<sub>3</sub> (426.7 mg  
 3 6.88 mmol, 0.43 mL, 16M), and 1.31g (0.013 mol, 0.74 mL, 18 M)  
 4 of H<sub>2</sub>SO<sub>4</sub> were slowly added. After 20 min, ice was added and  
 5 the resulting mixture was extracted with EtOAc. The combined  
 6 extracts were concentrated under reduced pressure to give a  
 7 yellow oil from which the title compound, a pale yellow solid, was  
 8 isolated by column chromatography (10% EtOAc / hexanes).  
 9 <sup>1</sup>H NMR (CDCl<sub>3</sub>) : δ 8.83 (1H, d, J = 2.6 Hz), 8.31 (1H, dd, J =  
 10 2.8, 8.9 Hz), 7.62 (1H, d, J = 8.7 Hz), 2.81 (2H, t, J = 6.5 Hz),  
 11 2.08 (2H, t, J = 6.5 Hz), 1.45 (6H, s).

12 3,4-dihydro-4,4-dimethyl-7-amino-naphthalen-1(2H)-one  
 13 (Compound D9)

14 A solution of 230.0 mg (1.05 mmol) 3,4-dihydro-4,4-  
 15 dimethyl-7-nitro-naphthalen-1(2H)-one (Compound D8) in 5.0 mL  
 16 of EtOAc was stirred at room temperature with a catalytic amount  
 17 of 10% Pd-C under 1 atm of H<sub>2</sub> for 24 h. The catalyst was  
 18 removed by filtration through a pad of Celite, and the filtrate  
 19 concentrated under reduced pressure to give the title compound  
 20 as a dark green oil.

21 <sup>1</sup>H NMR (CDCl<sub>3</sub>) : δ 7.30 (1H, d, J = 2.7 Hz), 7.22 (1H, d, J =  
 22 8.4 Hz), 6.88 (1H, dd, J = 2.7, 8.5 Hz), 2.70 (2H, t, J = 6.6 Hz),  
 23 1.97 (2H, t, J = 6.6 Hz), 1.34 (6H, s).

24 Ethyl 4-[(5,6-dihydro-5,5-dimethyl-8(7H)-one-naphthalen-2-  
 25 yl)azo]-benzoate (Compound D10)

26 To a solution of 198.7 mg (1.05 mmol) 3,4-dihydro-4,4-  
 27 dimethyl-7-amino-naphthalen-1(2H)-one (Compound D9) in 5.0  
 28 mL glacial acetic acid was added 180.0 mg (1.00 mmol) of ethyl 4-

1 nitrosobenzoate. The resulting solution was stirred overnight at  
2 room temperature, and then concentrated under reduced pressure.  
3 The product was isolated from the residual oil as a red solid, by  
4 column chromatography (15% EtOAc - hexanes).

5  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) :  $\delta$  8.57 (1H, d,  $J = 2.0$  Hz), 8.19 (2H, d,  $J =$   
6 8.4 Hz), 8.07 (1H, d,  $J = 8.0$  Hz), 7.94 (2H, d,  $J = 8.4$  Hz), 7.58  
7 (1H, d,  $J = 8.6$  Hz), 4.41 (2H, q,  $J = 7.1$  Hz), 2.79 (2H, t,  $J = 6.6$   
8 Hz), 2.07 (2H, t,  $J = 7.02$  Hz), 1.44 (6H, s), 1.42 (3H, t,  $J = 7.1$   
9 Hz).

10 Ethyl 4-[(5,6-dihydro-5,5-dimethyl-8-(trifluoromethylsulfonyl)oxy-  
11 naphthalen-2-yl)azo]-benzoate (Compound D11)

12 To a solution of 90.4 mg sodium bis(trimethylsilyl)amide  
13 (0.48 mmol, 0.48 mL of a 1.0 M THF solution) in 2.0 mL THF at  
14  $-78^\circ\text{C}$ , was added 153.0 mg (0.437 mmol) of ethyl 4-[(5,6-dihydro-  
15 5,5-dimethyl-8(7H)-one-naphthalen-2-yl)azo]-benzoate (Compound  
16 D10) in 2.0 mL THF. The dark red solution was stirred at  $-78^\circ\text{C}$   
17 for 30 min and then 204.0 mg (0.520 mmol) 2-[*N,N*-  
18 bis(trifluoromethylsulfonyl)amino]-5-chloropyridine was added as a  
19 solution in 2.0 mL THF. The reaction mixture was allowed to  
20 warm to room temperature and after 3 h was quenched by the  
21 addition of  $\text{H}_2\text{O}$ . The organic layer was concentrated to a red oil  
22 under reduced pressure. The product was isolated by column  
23 chromatography (25% EtOAc / hexanes) as a red oil.  
24  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) :  $\delta$  8.21 (2H, d,  $J = 8.6$  Hz), 7.96 (2H, d,  $J =$   
25 8.6 Hz), 7.94 (2H, m), 7.49 (1H, d,  $J = 8.2$  Hz), 6.08 (1H, t,  $J =$   
26 2.5 Hz), 4.42 (2H, q,  $J = 7.1$  Hz), 2.49 (2H, d,  $J = 4.8$  Hz), 1.44  
27 (3H, t,  $J = 7.1$  Hz), 1.38 (6H, s).

28 Ethyl 4-[(5,5-dimethyl-8-(2-thienyl)-5,6-dihydronaphthalen-2-

1 yl)azo]benzoate (Compound D12)

2 To a cold solution (-78 °C) of thiophene (0.07 ml, 0.75  
3 mmol) in 1.5 ml of THF was added t-BuLi (0.457 ml, 0.75 mmol,  
4 1.7 M in pentane) and stirred for 2 h. To this solution, ZnCl<sub>2</sub> (168  
5 mg, 1.2 mmol) in 1.5 ml of THF was added. The resulting  
6 solution was warmed to room temperature, stirred for 1h and was  
7 added (via cannula) to a solution of ethyl 4-[(5,6-dihydro-5,5-  
8 dimethyl-8-trifluoromethylsulfonyloxy-naphthalen-2-  
9 yl)azo]benzoate (Compound D11, 150 mg, 0.30 mmol) and  
10 tetrakis(triphenylphosphine)palladium(0) (10.6 mg) in 2.5 ml of  
11 THF. The resulting mixture was heated at 50 °C for 2.5 h. The  
12 reaction was diluted with sat. aqueous NH<sub>4</sub>Cl and extracted with  
13 ethyl acetate. The combined organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>  
14 and concentrated to an oil. The crude product was purified by  
15 flash chromatography (silica, ethyl acetate : hexane 5 : 95) to  
16 afford the title compound as a red foam.

17 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.40 (s, 6H), 1.44 (t, J = 7.14 Hz, 3H), 2.41  
18 (d, J = 4.82 Hz, 2H), 4.42 (q, J = 7.14 Hz, 2H), 6.29 (t, J = 4.83  
19 Hz, 1H), 7.14 (m, 2H), 7.32 (dd, J = 1.52, 3.36, 1H), 7.53 (d, J =  
20 8.31 Hz, 1H), 7.84 (dd, J = 2.08, 6.17 Hz, 1H), 7.92 (d, J = 8.60  
21 Hz, 2H), 8.03 (d, J = 2.07 Hz, 1H), 8.18 (d, J = 8.61 Hz, 2H).

22 4-[(5,5-Dimethyl-8-(2-thienyl)-5,6-dihydronaphthalen-2-  
23 yl)azo]benzoic acid (Compound D13)

24 Using the same procedure as for the preparation of 4-  
25 [(8(7H)-*anti*-(O-methyl oxime)-5,5-dimethyl-5,6-  
26 dihydronaphthalen-2-yl)azo]benzoic acid (Compound D4), ethyl 4-  
27 [(5,5-dimethyl-8-(2-thienyl)-5,6-dihydronaphthalen-2-  
28 yl)azo]benzoate (Compound 12, 100 mg, 0.258 mmol) was

1 converted into the title compound (red solid).

2  $^1\text{H}$  NMR (acetone- $d_6$ ):  $\delta$  1.40 (s, 6H), 2.43 (d,  $J$  = 4.83 Hz, 2H),  
3 2.82 (b, 1H), 6.32 (t,  $J$  = 4.88 Hz, 1H), 7.19 (m, 2H), 7.50 (d,  $J$  =  
4 4.88 Hz, 1H), 7.65 (d,  $J$  = 8.24 Hz, 1H), 7.95 (m, 4H), 8.21 (d,  $J$   
5 = 8.55 Hz, 2H).

6 3,4-dihydro-4,4-dimethyl-7-acetyl-naphthalen-1(2H)-one  
7 (Compound D14a); and 3,4-dihydro-4,4-dimethyl-6-acetyl-  
8 naphthalen-1(2H)-one (Compound D14b)

9 To a cold (0° C) mixture of aluminum chloride (26.3 g,  
10 199.0 mmols) in dichloromethane (55 mL) were added  
11 acetylchloride (15 g, 192 mmols) and 1,2,3,4-tetrahydro-1,1-  
12 dimethylnaphthalene (24.4g, 152mmols) in dichloromethane (20  
13 mL) over 20 minutes. The reaction mixture was warmed to  
14 ambient temperature and stirred for 4 h. Ice (200 g) was added to  
15 the reaction flask and the mixture diluted with ether (400 mL).  
16 The layers were separated and the organic phase was washed with  
17 10% HCl (50 mL), water (50 mL), 10% aqueous sodium  
18 bicarbonate, and saturated aqueous NaCl (50 mL) and thereafter  
19 dried over  $\text{MgSO}_4$ . The solvent was removed by distillation to  
20 afford a yellow oil which was dissolved in benzene (50 mL).

21 To a cold (0° C) solution of acetic acid (240 mL) and  
22 acetic anhydride (120 mL) was added chromiumtrioxide (50 g, 503  
23 mmols) in small portions over 20 mins under argon. The mixture  
24 was stirred for 30 mins at 0° C and diluted with benzene (120  
25 mL). The benzene solution prepared above, was added with  
26 stirring via an addition funnel over 20 mins. After 8 h, the  
27 reaction was quenched by the careful addition of isopropanol (50  
28 mL) at 0° C, followed by water (100 mL). After 15 mins, the



1 reaction mixture was diluted with ether (1100 mL) and water (200  
2 mL), and then neutralized with solid sodium bicarbonate (200 g).  
3 The ether layer was washed with water (100 mL), and saturated  
4 aqueous NaCl (2 x 100 mL), and dried over MgSO<sub>4</sub>. Removal of  
5 the solvent under reduced pressure afforded a mixture of the  
6 isomeric diketones which were separated by chromatography ( 5%  
7 EtOAc / hexanes).

8 (Compound D14a): <sup>1</sup>H NMR (CDCl<sub>3</sub>) : d 8.55 (1H, d, J = 2.0  
9 Hz), 8.13 (1H, dd, J = 2.0, 8.3 Hz), 7.53 (1H, d, J = 8.3 Hz), 2.77  
10 (2H, t, J = 6.6 Hz), 2.62 (3H, s), 2.05 (2H, t, J = 6.6 Hz), 1.41  
11 (6H, s).

12 (Compound D14b): <sup>1</sup>H NMR (CDCl<sub>3</sub>) : d 8.10 (1H, d, J = 8.1  
13 Hz), 8.02 (1H, d, J = 1.6 Hz), 7.82 (1H, dd, J = 1.6, 8.1 Hz), 2.77  
14 (2H, t, J = 7.1 Hz), 2.64 (3H, s), 2.05 (2H, t, J = 7.1 Hz), 1.44  
15 (6H, s).

16 6-(2-methyl-1,3-dioxolan-2-yl)-3,4-dihydro-4,4-dimethylnaphthalen-  
17 1(2H)-one (Compound D15)

18 A solution of 1.80 g (8.34 mmol) of a 1:5 mixture of 3,4-  
19 dihydro-4,4-dimethyl-7-acetyl-naphthalen-1(2H)-one (Compound  
20 D14a); and 3,4-dihydro-4,4-dimethyl-6-acetyl-naphthalen-1(2H)-  
21 one (Compound D14b) in 50 mL benzene was combined with  
22 517.7 mg (8.34 mmol) of ethylene glycol and 20.0 mg (0.11 mmol)  
23 of *p*-toluenesulfonic acid monohydrate. The resulting solution was  
24 heated to reflux for 18 h, cooled to room temperature, and  
25 concentrated under reduced pressure. The title compound was  
26 isolated by column chromatography (10% EtOAc - hexanes) as a  
27 colorless oil.

28 <sup>1</sup>H NMR (CDCl<sub>3</sub>) : δ 8.01 (1H, d, J = 8.2 Hz), 7.51 (1H, s), 7.43

1 (1H, dd,  $J = 1.7, 6.4$  Hz), 4.07 (2H, m), 3.79 (2H, m), 2.74 (2H, t,  
2  $J = 6.5$  Hz), 2.04 (2H, t,  $J = 7.1$  Hz), 1.67 (3H, s), 1.46 (6H, s).

3 (+/-) 6-(2-Methyl-1,3-dioxolan-2-yl)]-1,2,3,4-tetrahydro-4,4-

4 dimethyl-1-hydroxy-

5 1-(carboethoxymethyl)-naphthlene (Compound D16)

6 Using the same procedure as for the preparation of ethyl 4-  
7 [(5,6,7,8-tetrahydro-5,5-dimethyl-8-hydroxy-8-  
8 (carboethoxymethyl)naphthalen-2-yl)azo]benzoate, 6-(2-methyl-1,3-  
9 dioxolan-2-yl)]-3,4-dihydro-4,4-dimethylnaphthalen-1(2H)-one  
10 (Compound D1), 6-(2-methyl-1,3-dioxolan-2-yl)-3,4-dihydro-4,4-  
11 dimethylnaphthalen-1(2H)-one (Compound D15, 300 mg, 1.15  
12 mmol) was converted to the title product (321 mg, light yellow  
13 oil), using zinc dust (0.5 g, pretreated) and bromo ethyl acetate  
14 (0.256 ml, 0.30 mmol) in 10 ml of benzene.

15  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.29 (t,  $J = 7.08$  Hz, 3H), 1.30 (s, 3H), 1.32  
16 (s, 3H), 1.65 (s, 3H), 2.06 (s, 2H), 2.80 (q,  $J = 1.45$  Hz, 2H), 3.77  
17 (m, 2H), 4.05 (m, 2H), 4.13 (q,  $J = 7.14$  Hz, 2H), 4.22 (q,  $J =$   
18 7.14 Hz, 2H), 7.30 (dd,  $J = 1.71, 6.54$  Hz, 1H), 7.42 (d,  $J = 1.77$   
19 Hz, 1H), 7.53 (d,  $J = 8.18$  Hz, 1H).

20 3,4-Dihydro-4,4-dimethyl-1-(carboethoxymethyl)-6-acetyl-  
21 naphthalene (Compound D17)

22 A solution of (+/-) 6-(2-methyl-1,3-dioxolan-2-yl)-1,2,3,4-  
23 tetrahydro-4,4-dimethyl-1-hydroxy-1-(carboethoxymethyl)-  
24 naphthlene ((Compound D16, 321 mg, 0.90 mmol) and catalytic  
25 amount of TsOH in 20 ml of benzene was refluxed for 12 h.  
26 During the reaction the water generated from the reaction was  
27 periodically removed by a Dean-Stark trap. The solvent was  
28 removed and the residue was purified by column chromatography

1 (silica, ethyl acetate/hexane (1/3)) to give the title compound as an  
2 oil (215 mg).

3  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.20 (t,  $J = 7.14$  Hz, 3H), 1.33 (s, 6H), 2.30  
4 (d,  $J = 3.42$  Hz, 2H), 2.60 (s, 3H), 3.50 (s, 2H), 4.16 (q,  $J = 7.14$   
5 Hz, 2H), 6.06 (t,  $J = 4.64$  Hz, 1H), 7.28 (d,  $J = 2.80$  Hz, 1H), 7.76  
6 (,  $J = 1.34$ , 6.10 Hz, 1H), 7.93 (s, 1H).

7 (E)-4-[3-(3,4-dihydro-4,4-dimethyl-1-(carboethoxymethyl))-  
8 naphthalen-6-yl]-prop-1-en-3-one]benzoic acid (Compound D18)

9 To a solution of 3,4-dihydro-4,4-dimethyl-1-  
10 (carboethoxymethyl)-6-acetyl-naphthalene ((Compound D17, 25  
11 mg, 0.10 mmol) and 4-carboxybenzaldehyde (17 mg, 0.13 mmol) in  
12 2 ml of MeOH was added aqueous NaOH (0.75 ml, 12%). The  
13 reaction mixture was stirred at room temperature for overnight  
14 and quenched by addition of 10 % HCl to  $\text{pH} = 4.0$ . The solvent  
15 was removed and extracted ethyl acetate, the combined organic  
16 layer was washed with water. The organic layer was dried and  
17 concentrated to a white solid. This white solid was dissolved in 1  
18 ml of DMF. To this solution was added DMAP (15.2 mg, 0.12  
19 mmol), EDC (22 mg, 0.11 mmol) and 0.5 ml EtOH. The reaction  
20 mixture was stirred at room temperature for 5 h and concentrated  
21 in vacuo. The residue was passed through a chromatographic  
22 column with ethyl acetate/hexane (1/9) to give the title compound  
23 as a light tan solid.

24  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.21 (t,  $J = 7.14$  Hz, 3H), 1.36 (s, 6H), 1.42  
25 (t,  $J = 7.14$  Hz, 3H), 2.33 (d,  $J = 4.46$  Hz, 2H), 4.13 (q,  $J = 7.14$   
26 Hz, 2H), 4.41 (q,  $J = 7.14$  Hz, 2H), 6.09 (t,  $J = 4.79$  Hz, 1H), 7.32  
27 (d,  $J = 8.05$  Hz, 1H), 7.60 (d,  $J = 15.6$  Hz, 1H), 7.70 (d,  $J = 8.36$   
28 Hz, 2H), 7.80 (s, 1H), 7.85 (d,  $J = 8.12$  Hz, 1H), 8.00 (d,  $J = 1.77$

1 Hz, 1H), 8.10 (d, J = 8.36 Hz, 2H).

2 3,4-Dihydro-4,4-dimethyl-6-acetyl-1-(1,1-dimethylethyl)naphthalene  
3 (Compound D19)

4 To a solution of 6-(2-methyl-1,3-dioxolan-2-yl)]-3,4-dihydro-  
5 4,4-dimethylnaphthalen-1(2H)-one ((Compound D15, 353 mg, 1.36  
6 mmol) in 3 ml of dry ether at -78 °C was added dropwise t-BuLi  
7 (1 ml, 1.7 mmol, 1.7 M solution in pentane). This clear light  
8 yellow solution was left at -78 °C for 30 min. Then, freshly  
9 distilled SOCl<sub>2</sub> (0.15 ml, 2.0 mmol) was added. The reaction  
10 mixture was stirred at -78 °C for additional 30 min and thereafter  
11 slowly warmed to room temperature. The reaction was quenched  
12 by addition of saturated NH<sub>4</sub>Cl. The white solids were removed  
13 by filtration and the clear solution was concentrated to an oil, and  
14 purified by column chromatography with ethyl acetate/hexane  
15 (1/10) to give the title compound as a yellow oil.

16 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.92 (d, J = 1.79 Hz, 1H), 7.76 (dd, J =  
17 1.80, 8.23 Hz, 1H), 7.73 (d, J = 8.23 Hz, 1H), 6.10 (t, J = 4.98  
18 Hz, 1H), 2.58 (s, 3H), 2.18 (d, J = 5.00 Hz, 2H), 1.34 (s, 9H), 1.25  
19 (s, 6H).

20

21 (E)-4-[3-(3,4-Dihydro-4,4-dimethyl-1-(1,1-dimethyl-ethyl)naphth-6-  
22 yl)-prop-1-en-3-one]benzoic acid (Compound D20)

23 To a solution of 3,4-dihydro-4,4-dimethyl-6-acetyl-1-(1,1-  
24 dimethylethyl)naphthalene (Compound D19, 60 mg, 0.234 mmol)  
25 and 4-carboxybenzaldehyde (35 mg, 0.233 mmol) in 5 ml of EtOH  
26 and 1 ml of THF was added 3 ml of 1 M aqueous NaOH. The  
27 yellow reaction mixture was left overnight when it turned red and  
28 then quenched with 6% HCl until it became yellow again. The

1 solvent was removed and the residue was dissolved in thyl  
2 acetate. The organic solution was washed with brine and dried.  
3 After evaporation of the solvent, the residue was purified by  
4 recrystallization from ethyl acetate to give 28 mg title compound  
5 as yellow crystals.

6  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  8.15 (d,  $J = 8.31$  Hz, 2H), 8.00 (d,  $J = 1.80$   
7 Hz, 1H), 7.86 (dd,  $J = 1.83, 8.24$  Hz, 1H), 7.83 (d,  $J = 15.82$  Hz,  
8 1H), 7.78 (d,  $J = 8.48$  Hz, 1H), 7.74 (d,  $J = 8.31$  Hz, 2H), 7.65 (d,  
9  $J = 15.87$  Hz, 1H), 6.13 (t,  $J = 5.0$  Hz, 1H), 2.21 (d,  $J = 4.9$  Hz,  
10 2H), 1.38 (s, 9H), 1.30 (s, 6H).

11 6-Bromo-1(2H)-(propyliden-2-yl)-3,4-dihydro-4,4-  
12 dimethylnaphthalene (Compound D21)

13 To a mixture of  $\text{TiCl}_3$  (5 g, 32 mmol) of in 80 ml of dry  
14 DME under argon atmosphere was added in small portions  
15 lithium wire (0.80 g, 92 mmol). The reaction mixture was heated  
16 at  $85^\circ\text{C}$  for 1 h and then cooled to room temperature. To the  
17 above solution was added a mixture of 6-bromo-3,4-dihydro-4,4-  
18 dimethylnaphthalen-1(2H)-one (Compound H, 1.00 g, 4.0 mmol)  
19 in 10 ml of dry DME and 10 ml of dry acetone through a cannula.  
20 The resulting mixture was heated to reflux and was left for 12 h  
21 and then cooled to room temperature. The reaction mixture was  
22 diluted with 80 ml of hexane and then filtered through florisil.  
23 Purification by column chromatography with pure hexane as the  
24 eluent gave the title compound as a clear oil.  
25  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.23 (s, 6H), 1.60 t,  $J = 7.09$  Hz, 2H), 1.82  
26 (s, 3H), 1.92 (s, 3H), 2.49 (t,  $J = 6.60$  Hz, 2H), 7.10 (d,  $J = 8.30$   
27 Hz, 1H), 7.26 (dd,  $J = 1.95, 6.05$  Hz, 1H), 7.40 (d,  $J = 2.08$  Hz,  
28 1H).

1 6-Acetyl-1(2H)-(propyliden-2-yl)-3,4-dihydro-4,4-  
 2 dimethylnaphthalene (Compound D22)

3 To a solution of 6-bromo-1(2H)-(propyliden-2-yl)-3,4-  
 4 dihydro-4,4-dimethylnaphthalene (Compound D21, 910 mg, 3.3  
 5 mmol) and bis(triphenylphosphine)palladium(II) chloride (100 mg,  
 6 0.14 mmol) of in 50 ml of DMF under argon was added (1-  
 7 ethoxyvinyl)tributyl tin (1.713 ml, 5.07 mmol). The resulting  
 8 reaction mixture was heated at 85 °C for 48 h and cooled down to  
 9 room temperature. The reaction was quenched with 15 ml of 10%  
 10 HCl and then diluted with ethyl acetate. The organic layer was  
 11 washed with brine and dried over MgSO<sub>4</sub>. Purification by column  
 12 chromatography with pure hexane afforded the title compound as  
 13 a yellow oil (410 mg).  
 14 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.28 (s, 6H), 1.64 (t, J = 6.99 Hz, 2H), 1.86  
 15 (s, 3H), 1.97 (s, 3H), 2.53 (t, J = 6.6 Hz, 2H), 2.61 (s, 3H), 7.31  
 16 (d, J = 8.06 Hz, 1H), 7.74 (dd, J = 1.96, 6.10 Hz, 1H), 7.92 (d, J  
 17 = 1.89 Hz, 1H).

18  
 19 (E)-4[3-{1(2H)-(propyliden-2-yl)-3,4-dihydro-4,4-  
 20 dimethylnaphthalen-6-yl}-prop-1-en-3-one]benzoic acid  
 21 (Compound D23)

22 The title compound can be obtained by following the  
 23 procedure employed for the preparation of (E)-4-[3-(3,4-dihydro-  
 24 4,4-dimethyl-1-(carboethoxymethyl)-naphthalen-6-yl)-prop-1-en-3-  
 25 one]benzoic acid (Compound D18).

26 (+/-) 1-Hydroxy-6-(1,3-dioxolan-2-yl)]-1,2,3,4-tetrahydro-4,4-  
 27 dimethylnaphthalene (Compound D24)

28 To a solution of 6-(1,3-dioxolan-2-yl)]-3,4-dihydro-4,4-

1 dimethylnaphthalen-1(2H)-one (Compound D15, 110 mg, 0.42  
 2 mmol) in 6 ml of EtOH at 0 °C was added NaBH<sub>4</sub> (16 mg, 0.42  
 3 mmol). The reaction mixture was stirred for 4 h and kept in a  
 4 freezer for overnight. The reaction was quenched with slow  
 5 addition of cold water and extracted with ethyl acetate. The  
 6 organic layer was dried and concentrated to an oil. Purification by  
 7 column chromatography with ethyl acetate/hexane (1/3) gave the  
 8 title compound as a clear oil.

9 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.26 (s, 3H), 1.34 (s, 3H), 1.65 (s, 3H), 1.61  
 10 (m, 1H), 1.89 (m, 2H), 2.07 (m, 1H), 3.74 (m, 2H), 4.05 (m, 2H),  
 11 4.74 (t, J = 5.10 Hz, 1H), 7.30 (dd, J = 1.65, 6.16, 1H), 7.41 (d, J  
 12 = 7.94 Hz, 1H), 7.45 (d, J = 1.83 Hz, 1H).

13 (+/-) 1-Hydroxy-6-acetyl-1,2,3,4-tetrahydro-4,4-dimethyl-  
 14 naphthalene (Compound D25)

15 A solution of 1-hydroxy-6-(1,3-dioxolan-2-yl)-1,2,3,4-  
 16 tetrahydro-4,4-dimethylnaphthalene (Compound D24, 54.9 mg,  
 17 0.21 mmol) in 3 ml of 10% HCl and 3 ml THF was heated at 100  
 18 °C for 1.5 h and cooled to room temperature. The reaction  
 19 mixture was diluted with ethyl acetate and neutralized with sat.  
 20 NaHCO<sub>3</sub>. The organic layer was further washed with brine, dried  
 21 and concentrated to an oil. Purification by column  
 22 chromatography (silica) with ethyl acetate/hexane (1/9) gave the  
 23 title compound as a clear oil (24.8 mg).

24 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.29 (s, 3H), 1.34 (s, 3H), 1.66 (m, 1H), 1.89  
 25 (m, 2H), 2.10 (m, 1H), 2.56 (s, 3H), 4.75 (t, J = 4.90, 1H), 7.54 (d,  
 26 J = 8.18 Hz, 1H), 7.75 (dd, J = 1.83, 6.29 Hz, 1H), 7.94 (d, J =  
 27 1.77 Hz, 1H).

28 (+/-) 1-(Methoxymethoxy)-6-acetyl-1,2,3,4-tetrahydro-4,4-

1 dimethyl-naphthalene (Compound D26)

2 A solution of (+/-) 1-hydroxy-6-acetyl-1,2,3,4-tetrahydro-4,4-  
3 dimethyl-naphthalene (Compound D25, 24.8 mg, 0.11 mmol),  
4 chloromethyl methyl ether (0.12 mmol), triethyl amine (0.02 ml,  
5 0.13 mmol) and catalytic amount of tetrabutylammonium bromide  
6 in 2 ml of CH<sub>2</sub>Cl<sub>2</sub> was stirred at room temperature for 5 h.  
7 Purification by column chromatography (silica) with ethyl  
8 acetate/hexane (1/10) afforded the title compound as an oil (17.8  
9 mg).

10 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.95 (d, J = 1.7 Hz, 1H), 7.73 (dd, J = 1.7,  
11 8.4 Hz, 1H), 7.44 (d, J = 8.4 Hz, 1H), 4.88 (d, J = 6.41 Hz, 1H),  
12 4.76 (d, J = 6.41 Hz, 1H), 4.67 (m, 1H), 3.48 (s, 3H), 2.59 (s, 3H),  
13 2.00 (m, 3H), 1.58 (m, 1H), 1.37 (s, 3H), 1.29 (s, 3H).

14 (E)-4-[3-(1,2,3,4-Tetrahydro-4,4-dimethyl-1-(methoxymethoxy))-  
15 naphthalen-6-yl]-prop-1-en-3-one]benzoic acid (Compound D27)

16 The title compound can be prepared by following the  
17 procedure employed for the preparation of (E)-4-[3-(3,4-dihydro-  
18 4,4-dimethyl-1-(carboethoxymethyl)-naphthalen-6-yl)-prop-1-en-3-  
19 one]benzoic acid (Compound D18).

20 6-Acetyl-1(2H)-(O-methyl oxime)-3,4-dihydro-4,4-  
21 dimethylnaphthalene (Compound D28)

22 To a solution of 6-(1,3-dioxolan-2-yl)-3,4-dihydro-4,4-  
23 dimethylnaphthalen-1(2H)-one (Compound D15, 100 mg, 0.38  
24 mmol), NaOAc (78.8 mg, 0.95 mmol) in 5 ml of EtOH and 2 ml  
25 of THF was added methoxyamine hydrochloride (32.1 mg, 0.38  
26 mmol). The resulting mixture was stirred at room temperature for  
27 overnight. The solvent was removed and the residue was dissolved  
28 in ethyl acetate (5 mL) and washed with saturated NaHCO<sub>3</sub>.



1 water and brine. The solvent was distilled off and the crude  
 2 product was purified by column chromatography with ethyl  
 3 acetate/hexane (1/3) to give the title compound as an oil.  
 4 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.42 (s, 6H), 2.03 (t, J = 6.07 Hz, 2H), 2.24  
 5 (s, 3H), 2.74 (t, J = 6.71 Hz, 2H), 4.04 (s, 3H), 7.56 (dd, J = 1.52,  
 6 6.72 Hz, 1H), 7.70 (d, J = 1.75 Hz, 1H), 8.02 (d, J = 8.24 Hz,  
 7 1H).

8 (E)-4[3-{1(2H)-(O-methyl oxime)-3,4-dihydro-4,4-  
 9 dimethylnaphthalen-6-yl}-prop-1-en-3-one]benzoic acid  
 10 (Compound D29)

11 The title compound can be prepared by following the  
 12 procedure employed for the preparation of (E)-4-[3-(3,4-dihydro-  
 13 4,4-dimethyl-1-(carboethoxymethyl)-naphthalen-6-yl)-prop-1-en-3-  
 14 one]benzoic acid (Compound D18).

15 3,4-dihydro-1-(trifluoromethylsulfonyl)oxy-4,4-dimethyl-6-(2-(2-  
 16 methyl-1,3-dioxolany))naphthalene (Compound D30)

17 To a cold solution (-78° C) of 232.7 mg (1.267 mmol) of sodium  
 18 bis(trimethylsilyl)amide in 2.0 ml of THF was added a solution of  
 19 300.0 mg (1.154 mmol) of 6-(1,3-dioxolan-2-yl)-3,4-dihydro-4,4-  
 20 dimethylnaphthalen-1(2H)-one (Compound D15) in 4.0 ml of  
 21 THF. The reaction mixture was stirred at -78° C for 30 minutes  
 22 and then a solution of 498.0 mg (1.269 mmol) of 5-chloro(2-bis-  
 23 trifluoromethylsulfonyl)imide in 3.0 ml of THF was added. After  
 24 stirring at -78° C for 1 hour, the solution was warmed to 0° C and  
 25 stirred for 12 hours. The reaction was quenched by the addition  
 26 of saturated aqueous NH<sub>4</sub>Cl. The mixture was extracted with  
 27 EtOAc (50 ml) and the combined organic layers were washed with  
 28 saturated aqueous NaHCO<sub>3</sub>, water, and brine. The organic phase

1 was dried over  $\text{Na}_2\text{SO}_4$  and then concentrated *in vacuo* to a  
2 yellow oil. Purification by column chromatography (silica, 10%  
3 EtOAc-hexanes) yielded the title compound as a clear yellow oil.  
4  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.43 (1H, s), 7.38 (2H, m), 5.95 (1H, t,  $J$  =  
5 4.8 Hz), 4.07 (2H, m) 3.77 (2H, m) 2.42 (2H, d,  $J$  = 4.9 Hz), 1.66  
6 (3H, s), 1.32 (6H, s).

7 3,4-dihydro-1-(2-thienyl)-4,4-dimethyl-6-(2-(2-methyl-1,3-  
8 dioxolanyl))naphthalene (Compound D32)

9 A solution of 2-thienyllithium was prepared by the addition  
10 of 106.9 mg (0.67 ml, 1.67 mmol) of n-butyl lithium (2.5 M  
11 solution in hexanes) to a cold solution ( $0^\circ\text{C}$ ) of 140.0 mg (1.67  
12 mmol) of thiophene in 1.0 ml of THF. After stirring for 3 h a  
13 solution of 364.0 mg (2.67 mmol) of zinc chloride in 2.0 ml of  
14 THF was added. The resulting solution was warmed to room  
15 temperature, stirred for 30 minutes, and added via cannula to a  
16 solution of 262.0 mg (0.668 mmol) of 3,4-dihydro-1-  
17 (trifluoromethylsulfonyl)oxy-4,4-dimethyl-6-(2-(2-methyl-1,3-  
18 dioxolanyl))naphthalene (Compound D30) and 30 mg (0.03 mmol)  
19 of tetrakis(triphenylphosphine)palladium(0) in 2.0 ml of THF.  
20 The resulting solution was heated at  $50^\circ\text{C}$  for 12 h, cooled to  
21 room temperature and diluted with saturated aqueous  $\text{NH}_4\text{Cl}$ .  
22 The mixture was extracted with EtOAc and the combined organic  
23 layers were washed with water and brine. The organic phase was  
24 dried over  $\text{Na}_2\text{SO}_4$  and concentrated *in vacuo* to a yellow oil.  
25 Purification by column chromatography (10% EtOAc-hexanes)  
26 yielded the title compound as a yellow solid.  
27  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.48 (1H, d,  $J$  = 1.8 Hz), 7.34 (1H, d,  $J$  =  
28 7.9 Hz), 7.28 (2H, m), 7.08 (2H, m), 6.18 (1H, t,  $J$  = 4.8 Hz),

1 4.06 (2H, m), 3.82 (2H, m), 2.34 (2H, d,  $J = 4.8$  Hz), 1.70 (3H, s),  
 2 1.34 (6H, s).

3 3,4-dihydro-1-(2-thienyl)-4,4-dimethyl-6-acetylnaphthalene  
 4 (Compound D33)

5 A solution of 3,4-dihydro-1-(2-thienyl)-4,4-dimethyl-6-(2-(2-  
 6 methyl-1,3-dioxolanyl)naphthalene (Compound D32, 103.0 mg,  
 7 0.32 mmol) in 4.0 mL THF and 4.0 mL 10% aqueous HCl was  
 8 refluxed for 1.5 h. Upon cooling to room temperature, the  
 9 reaction mixture was diluted with EtOAc and washed with water  
 10 and saturated aqueous NaCl. The organic layer was dried over  
 11  $\text{MgSO}_4$  and the solvents were removed under reduced pressure to  
 12 give the title compound as a colorless oil after column  
 13 chromatography (10% EtOAc-hexanes).

14  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) :  $\delta$  7.98 (1H, d,  $J = 1.8$  Hz), 7.75 (1H, dd,  $J =$   
 15 1.8, 8.1 Hz), 7.46 (1H, d,  $J = 8.1$  Hz), 7.29 (1H, d,  $J = 5.0$  Hz),  
 16 7.09 (2H, m), 6.32 (1H, t,  $J = 4.8$  Hz), 2.61 (3H, s), 2.38 (2H, d,  $J$   
 17  $= 4.9$  Hz), 1.38 (6H, s).

18 4-[3-oxo-3-(7,8-dihydro-5-(2-thienyl)-8,8-dimethyl-2-naphthalenyl)-  
 19 1-propenyl]-benzoic acid (Compound D34)

20 To a solution of 62.6 mg (0.222 mmol) 3,4-dihydro-1-(2-  
 21 thienyl)-4,4-dimethyl-6-acetylnaphthalene (Compound D33) in 4.0  
 22 mL of MeOH were added 33.4 mg (0.222 mmol) of 4-carboxy  
 23 benzaldehyde, and 240.0 mg (6.00 mmol; 2.0 mL of 3M aqueous  
 24 NaOH). The resulting solution was stirred at room temperature  
 25 for 12 h, concentrated under reduced pressure, and the residual  
 26 oil dissolved in EtOAc. The solution was treated with 10% HCl,  
 27 and the organic layer washed with  $\text{H}_2\text{O}$ , and saturated aqueous  
 28 NaCl, before being dried over  $\text{Na}_2\text{SO}_4$ . Removal of the solvents

1 under reduced pressure gave the title compound as a pale green  
2 solid after recrystallization from EtOH.

3  $^1\text{H}$  NMR (acetone- $d_6$ ) :  $\delta$  8.16 (1H, s), 8.10 (1H, d,  $J$  = 8.4 Hz),  
4 8.00 (5H, m), 7.84 (1H, d,  $J$  = 15.5 Hz), 7.48 (2H, m), 7.14 (2H,  
5 m), 6.36 (1H, t,  $J$  = 4.8 Hz), 2.83 (1H, s), 2.43 (2H, d,  $J$  = 4.8  
6 Hz), 1.39 (6H, s).

7 Methyl-5,5-dimethyl-5,6-dihydro-naphthalen-8(7H)-one-2-  
8 carboxylate (Compound E2)

9 A degassed (with carbonmonoxide) solution of 2-bromo-5,5-  
10 dimethyl-5,6-dihydro-naphthalen-8(7H)-one (Compound G),  
11 palladium(II)-bis(triphenylphosphine)chloride (277 mg, 0.4 mmol),  
12 1,3-bis(diphenylphosphino)-propane (325 mg, 0.8 mmol), DMSO  
13 (30 mL), methanol (15 mL) and triethylamine (15 mL) was placed  
14 in an oil bath (70° C), under carbonmonoxide atmosphere) for  
15 16h. After dilution with water the mixture was extracted with ethyl  
16 acetate. The organic layer was washed with water, 10% HCl,  
17 saturated sodiumbicarbonate and brine. The organic layer was  
18 dried over  $\text{MgSO}_4$ , and the solvent was removed by distillation.  
19 The residual crude material was purified by flash chromatography  
20 (silica, 1:4 ethyl acetate : hexane) to afford the title compound as  
21 a white solid.

22  $^1\text{H}$ NMR ( $\text{CDCl}_3$ ) :  $\delta$  1.42 (s, 6H), 2.05 (t,  $J$  = 6.6 Hz, 2H), 2.77  
23 (dd,  $J$  = 6.6, 2H), 3.93 (s, 3H), 7.52 (d,  $J$  = 8.3 Hz, 1H), 8.17 (dd,  
24  $J$  = 1.8, 8.3 Hz, 1H), 8.67 (d,  $J$  = 1.8 Hz, 1H).

25 5,5-Dimethyl-5,6-dihydro-naphthalen-8(7H)-one-2-carboxylic acid  
26 (Compound E3)

27 To a solution of methyl-5,5-dimethyl-5,6-dihydro-  
28 naphthalen-8(7H)-one-2-carboxylate (Compound E2, 1.05 g, 4.5

1 mmol) in 10 mL of ethanol and THF (10 mL) was added  
2 sodiumhydroxide 9 mL (1M solution). The solution was stirred for  
3 16 h and thereafter acidified with 10% HCl. The mixture was  
4 extracted with ethyl acetate, the combined organic layer was  
5 washed with water and brine, and dried over MgSO<sub>4</sub>. The solvent  
6 was distilled off under reduced pressure to afford the title  
7 compound as a white solid.

8 <sup>1</sup>H NMR (Acetone-D<sub>6</sub>) : δ 1.44 (s, 6H), 2.07 (t, J = 6.7 Hz, 2H),  
9 2.73 (t, J = 6.7 Hz, 2H), 7.70 (d, J = 8.2 Hz, 1H), 8.19 (dd, J =  
10 1.9, 8.2 Hz, 1H), 8.57 (d, J = 1.9 Hz, 1H).

11 Methyl 5,5-dimethyl-5,6-dihydro-8-(trifluoromethylsulfonyl)oxy-  
12 naphthalene -2-carboxylate (Compound E4)

13 To a solution of sodium bis(trimethylsilyl)amide (550.1 mg,  
14 3.00 mmol, 3.0 mL of a 1.0 M solution in THF) in 5.0 mL of THF  
15 at -78 °C was added 620.0 mg (2.67 mmol) of methyl-5,5-dimethyl-  
16 5,6-dihydro-naphthalen-8(7H)-one-2-carboxylate (Compound E2)  
17 in 8.0 mL of THF. After 30 min a solution of 1.15 g (2.94 mmol)  
18 of 2-N,N-bis(trifluoromethylsulfonyl)amino-5-chloropyridine in 6.0  
19 mL of THF was added. Stirring for 45 min at -78 °C was  
20 followed by warming to room temperature and stirring for 5 h.  
21 The reaction was quenched by the addition of saturated aqueous  
22 NH<sub>4</sub>Cl and extracted with EtOAc. The combined organic layers  
23 were washed with 5% aqueous NaOH and dried over MgSO<sub>4</sub>.  
24 Concentration of the dry solution under reduced pressure to an oil  
25 and column chromatography using 10% EtOAc-hexanes afforded  
26 the title compound as a yellow oil.  
27 <sup>1</sup>H NMR(CDCl<sub>3</sub>) : δ 1.33 (s, 6H), 2.45 (d, J = 4.8 Hz, 2H), 3.93  
28 (s, 3H), 6.03 (t, J = 4.8 Hz, 1H), 7.40 (d, J = 8.5 Hz, 1H), 8.00

1 (m, 2H).

2 Methyl 5,5-dimethyl-5,6-dihydro-8-(2-thienyl)-naphthalene-2-  
 3 carboxylate (Compound E5)

4 To a solution of 329.0 mg (3.93 mmol) of thiophene in 2.0  
 5 mL THF at 0 °C was added 251.8 mg (3.93 mmol, 1.56 mL of 2.5  
 6 M solution in hexanes) of n-butyllithium. After stirring for 3 h at  
 7 0 °C, a solution of 845.0 mg (6.28 mmol) of ZnCl<sub>2</sub> in 5.0 mL  
 8 THF was added and the resulting solution stirred for 30 minutes.  
 9 This solution was added to a second flask containing 570.0 mg  
 10 (1.57 mmol) of methyl 5,5-dimethyl-5,6-dihydro-8-  
 11 (trifluoromethylsulfonyl)oxy-naphthalene-2-carboxylate (Compound  
 12 E4) and 76.0 mg (0.063 mmol) of  
 13 tetrakis(triphenylphosphine)palladium(0) in 4.0 mL THF, and the  
 14 resulting solution was heated to 50 °C for 3 h. Upon cooling to  
 15 room temperature the reaction was quenched by the addition of  
 16 saturated aqueous NH<sub>4</sub>Cl. Extraction with EtOAc was followed  
 17 by washing of the combined organic layers with H<sub>2</sub>O and  
 18 saturated aqueous NaCl, and drying over MgSO<sub>4</sub>. The dry  
 19 solution was concentrated under reduced pressure and the title  
 20 compound was isolated from the residue as a yellow oil by column  
 21 chromatography (5-10% EtOAc / hexanes).  
 22 <sup>1</sup>H NMR(CDCl<sub>3</sub>): δ 1.34 (s, 6H), 2.35 (d, J = 4.9 Hz, 2H), 3.86  
 23 (s, 3H), 6.23 (t, J = 4.9 Hz, 1H), 7.06 (m, 2H), 7.28 (m, 1H), 7.43  
 24 (d, J = 8.0 Hz, 1H), 7.92 (dd, J = 1.7, 8.0 Hz, 1H), 8.06 (d, J =  
 25 1.7 Hz, 1H).  
 26 5,5-dimethyl-5,6-dihydro-8-(2-thienyl)-naphthalene-2-carboxylic  
 27 acid (Compound E6)

28 To a solution of methyl 5,5-dimethyl-5,6-dihydro-8-(2-

1 thienyl)-2-naphthalenecarboxylate (Compound E5, 430.0 mg, 1.44  
2 mmol) in 3.0 mL of EtOH and 3.0 mL THF was added NaOH  
3 (240.0 mg, 6.00 mmol; 3.0 mL of a 2N aqueous solution). The  
4 resulting solution was warmed to 35 °C for 6 h, cooled to room  
5 temperature and quenched with 1M HCl. The mixture was  
6 extracted with EtOAc and the combined organic layers washed  
7 with H<sub>2</sub>O and saturated aqueous NaCl before being dried over  
8 MgSO<sub>4</sub>. Removal of the solvents under reduced pressure  
9 afforded the title compound as a pale yellow solid.  
10 <sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 1.34 (s, 6H), 2.38 (d, J = 4.8 Hz, 2H), 6.25 t,  
11 J = 4.8 Hz, 1H), 7.12 (m, 3H), 7.45 (dd, J = 1.8, 4.7 Hz, 1H), 7.54  
12 (d, J = 8.0 Hz, 1H), 7.92 (dd, J = 1.8, 8.0 Hz, 1H), 8.06 (d, J =  
13 1.8 Hz, 1H).

14 Ethyl 4-[(5,5-dimethyl-5,6-dihydro-8-(2-thienyl)-naphthalen-2-  
15 yl)carboxamido]-benzoate (Compound E7)

16 A solution of 5,5-dimethyl-5,6-dihydro-8-(2-thienyl)-  
17 naphthalene-2-carboxylic acid (Compound E6, 180.0 mg, 0.638  
18 mmol), ethyl 4-aminobenzoate (137.0 mg, 0.829 mmol), 1-(3-  
19 dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (160.0  
20 mg, 0.829 mmol), and 4-N,N-dimethylaminopyridine (101.0 mg,  
21 0.829 mmol) in 6.0 mL DMF was stirred overnight at room  
22 temperature. EtOAc (100 mL) was added and the solution  
23 washed with H<sub>2</sub>O, 5% HCl, saturated aqueous NaHCO<sub>3</sub>, and  
24 saturated aqueous NaCl before being dried over MgSO<sub>4</sub>.  
25 Removal of the solvents under reduced pressure and column  
26 chromatography (10-25% EtOAc-hexanes) of the residual oil  
27 afforded the title compound as a colorless solid.  
28 <sup>1</sup>H NMR(CDCl<sub>3</sub>): δ 1.36 (s, 6H), 1.39 (t, J = 7.1 Hz, 3H), 2.38

1 (d,  $J = 4.8$  Hz, 2H), 4.36 (q,  $J = 7.1$  Hz, 2H), 6.27 (t,  $J = 4.8$  Hz,  
 2 1H), 7.09 (m, 2H), 7.29 (m, 1H), 7.48 (d,  $J = 8.0$  Hz, 1H), 7.68 (d,  
 3  $J = 8.8$  Hz, 2H), 7.76 (dd,  $J = 1.9, 8.0$  Hz, 1H), 7.83 (s, 1H), 7.88  
 4 (d,  $J = 1.9$  Hz, 1H), 8.03 (d,  $J = 8.8$  Hz, 2H).

5 4-[(5,5-Dimethyl-5,6-dihydro-8-(2-thienyl)-naphthalen-2-  
 6 yl)carboxamido]-benzoic acid (Compound E8)

7 To a solution of ethyl 4-[(5,5-dimethyl-5,6-dihydro-8-(2-  
 8 thienyl)-naphthalen-2-yl)carboxamido]-benzoate (Compound E7,  
 9 110.0 mg, 0.255 mmol) in 2.0 mL of EtOH and 1.0 mL THF was  
 10 added NaOH (80.0 mg, 2.00 mmol; 2.0 mL of a 1N aqueous  
 11 solution). After stirring overnight at room temperature the  
 12 reaction was quenched by the addition of 1M aqueous HCl. The  
 13 mixture was extracted with EtOAc and the combined organic  
 14 layers washed with H<sub>2</sub>O and saturated aqueous NaCl before being  
 15 dried over MgSO<sub>4</sub>. Removal of the solvents under pressure  
 16 afforded the title compound as a pale yellow solid.

17 <sup>1</sup>H NMR(acetone-d<sub>6</sub>):  $\delta$  1.34 (s, 6H), 2.38 (d,  $J = 4.9$  Hz, 2H),  
 18 6.27 (t,  $J = 4.9$  Hz, 1H), 7.12 (m, 2H), 7.44 (dd,  $J = 1.3, 5.0$  Hz,  
 19 1H), 7.55 (d,  $J = 8.0$  Hz, 1H), 7.88 (m, 3H), 8.02-7.91 (m, 3H),  
 20 9.75 (s, 1H).

21 Ethyl 4-[(5,5-dimethyl-5,6-dihydro-8-(2-thienyl)-naphthalen-2-  
 22 yl)carbonyl]oxy]-benzoate (Compound E9)

23 A solution of 5,5-dimethyl-5,6-dihydro-8-(2-thienyl)-  
 24 naphthalene-2-carboxylic acid (Compound E6, 50.0 mg, 0.177  
 25 mmol), ethyl 4-hydroxybenzoate (38.2 mg, 0.230 mmol), 1-(3-  
 26 dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (44.0 mg,  
 27 0.230 mmol), and 4-*N,N*-dimethylaminopyridine (28.0 mg, 0.230  
 28 mmol) in 2.0 mL DMF was stirred overnight at room temperature.



1 EtOAc (50 mL) was added and the solution washed with H<sub>2</sub>O,  
 2 5% HCl, saturated aqueous NaCO<sub>3</sub>, and saturated aqueous NaCl  
 3 before being dried over MgSO<sub>4</sub>. Removal of the solvents under  
 4 reduced pressure and column chromatography (10% EtOAc-  
 5 hexanes) of the residual oil afforded the title compound as a  
 6 colorless solid.

7 <sup>1</sup>H NMR(CDCl<sub>3</sub>): δ 1.36 (s, 6H), 1.39 (t, J = 7.2 Hz, 3H), 2.39  
 8 (d, J = 4.9 Hz, 2H), 4.38 (q, J = 7.2 Hz, 2H), 6.26 (t, J = 4.9 Hz,  
 9 1H), 7.09 (m, 2H), 7.25 (m, 2H), 7.49 (d, J = 8.2 Hz, 1H), 8.08  
 10 (m, 3H), 8.22(d, J = 1.8 Hz, 1H).

11 2-trimethylsilylethyl 4-[[[(5,5-dimethyl-5,6-dihydro-8-(2-thienyl)-  
 12 naphthalen-2-yl)carbonyl]oxy]-benzoate (Compound E10)

13 A solution of 5,5-dimethyl-5,6-dihydro-8-(2-thienyl)-  
 14 naphthalene-2-carboxylic acid (Compound E6, 79.0 mg, 0.280  
 15 mmol), 2-trimethylsilylethyl 4-hydroxybenzoate (73.3 mg, 0.308  
 16 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide  
 17 hydrochloride (70.0 mg, 0.364 mmol), and 4-*N,N*-  
 18 dimethylaminopyridine (44.5 mg, 0.364 mmol) in 2.0 mL DMF was  
 19 stirred overnight at room temperature. Et<sub>2</sub>O (100 mL) was added  
 20 and the solution washed with H<sub>2</sub>O, 5% HCl, saturated aqueous  
 21 NaCO<sub>3</sub>, and saturated aqueous NaCl before being dried over  
 22 MgSO<sub>4</sub>. Removal of the solvents under reduced pressure and  
 23 column chromatography (10% EtOAc-hexanes) of the residual oil  
 24 afforded the title compound as a colorless solid.  
 25 <sup>1</sup>H NMR(CDCl<sub>3</sub>): δ 0.10 (s, 9H), 1.15 (t, J = 8.2 Hz, 2H), 1.38 (s,  
 26 6H), 2.39 (d, J = 4.0 Hz, 2H), 4.43 (t, J = 8.2 Hz, 2H), 6.28 (t, J  
 27 = 4.0 Hz, 1H), 7.09 (m, 2H), 7.26 (m, 3H), 7.52 (d, J = 7.2 Hz,  
 28 1H), 8.09 (m, 3H), 8.22 (s, 1H).

1 4-[[[(5,5-Dimethyl-5,6-dihydro-8-(2-thienyl)-naphthalen-2-  
 2 yl)carbonyl]oxy]-benzoic acid (Compound E11)

3 To a solution of 2-trimethylsilylethyl 4-[[[(5,5-dimethyl-5,6-  
 4 dihydro-8-(2-thienyl)-naphthalen-2-yl)carbonyl]oxy]-benzoate  
 5 (Compound E10, 100.0 mg, 0.198 mmol) in 2.0 mL THF at room  
 6 temperature was added 155.3 mg of tetrabutylammonium fluoride  
 7 (0.594 mmol 0.6 mL of a 1M solution in THF). After stirring  
 8 overnight the reaction was diluted with EtOAc and washed with  
 9 H<sub>2</sub>O and saturated aqueous NaCl before being dried over  
 10 MgSO<sub>4</sub>. The solvents were removed under reduced pressure and  
 11 the residue washed with hot acetonitrile leaving the product as a  
 12 colorless solid.

13 <sup>1</sup>H NMR(acetone-d<sub>6</sub>): δ 1.37 (s, 6H), 2.42 (d, J = 4.8 Hz, 2H),  
 14 6.30 (t, J = 4.8 Hz, 1H), 7.14 (m, 2H), 7.37 (d, J = 8.6 Hz, 2H),  
 15 7.44 (dd, J = 1.1, 5.0 Hz, 1H), 7.65 (d, J = 8.1 Hz, 1H), 8.12 (m,  
 16 4H).

17 1(2H)-(Propyliden-2-yl)-3,4-dihydro-4,4-dimethylnaphthalene-7-  
 18 carboxylic acid (Compound E12)

19 To a cold ( -78 °C) solution of 7-bromo-1(2H)-(propyliden-  
 20 2-yl)-3,4-dihydro-4,4-dimethylnaphthalene (Compound A37, 640.0  
 21 mg, 2.30 mmol) in 20 mL THF was added t-butyllithium (294.7  
 22 mg, 4.60 mmol; 2.7 mL of a 1.7M solution in pentane). After 1 h  
 23 dry CO<sub>2</sub> gas was bubbled through the solution for 1 h. The  
 24 resulting mixture was allowed to warm to room temperature and  
 25 then quenched with 10% aqueous HCl. The mixture was  
 26 extracted with EtOAc and the combined organic layers washed  
 27 with H<sub>2</sub>O and saturated aqueous NaCl before being dried over  
 28 Na<sub>2</sub>SO<sub>4</sub>. Concentration of the dry solution under reduced

1 pressure and washing of the residue with hexanes afforded the  
2 title compound as a pale yellow solid.

3  $^1\text{H}$  NMR(acetone- $d_6$ ):  $\delta$  1.25 (s, 6H), 1.63 (t,  $J$  = 6.9 Hz, 2H),  
4 1.85 (s, 3H), 1.95 (s, 3H), 2.53 (t,  $J$  = 6.9 Hz, 2H), 7.43 (d,  $J$  =  
5 8.1 Hz, 1H), 7.82 (dd,  $J$  = 1.8, 8.1 Hz, 1H), 7.94 (d,  $J$  = 1.8 Hz,  
6 1H).

7 2-(Trimethylsilyl)ethyl-4-[(5,5-dimethyl-8(7H)-(propyliden-2-yl)-  
8 5,6-dihydronaphthalen-2-yl)]carbonyl}oxy]benzoate (Compound  
9 E13)

10 A solution of 5,5-dimethyl-5,6-dihydro-8(7H)-(1-propyliden-  
11 2-yl)-naphthalene-2-carboxylic acid (Compound E12, 70.0 mg,  
12 0.287 mmol), 2-trimethylsilyl ethyl 4-hydroxybenzoate (71.0 mg,  
13 0.298 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide  
14 hydrochloride (71.0 mg, 0.370 mmol), and 4-*N,N*-  
15 dimethylaminopyridine (45.0 mg, 0.370 mmol) in 2.0 mL DMF was  
16 stirred overnight at room temperature.  $\text{Et}_2\text{O}$  (100 mL) was added  
17 and the solution washed with  $\text{H}_2\text{O}$ , 5% HCl, saturated aqueous  
18  $\text{NaHCO}_3$ , and saturated aqueous NaCl before being dried over  
19  $\text{MgSO}_4$ . Removal of the solvents under reduced pressure and  
20 column chromatography (5% EtOAc-hexanes) of the residual oil  
21 afforded the title compound as a colorless oil.

22  $^1\text{H}$  NMR( $\text{CDCl}_3$ ):  $\delta$  0.09 (s, 9H), 1.14 (t,  $J$  = 8.4 Hz, 2H), 1.28 (s,  
23 6H), 1.66 (d,  $J$  = 6.9 Hz, 2H), 1.86 (s, 3H), 2.00 (s, 3H), 2.54 (t,  $J$   
24 = 6.9 Hz, 2H), 4.30 (t,  $J$  = 8.4 Hz, 2H), 7.28 (d,  $J$  = 8.7 Hz, 2H),  
25 7.43 (d,  $J$  = 8.1 Hz, 1H), 7.97 (dd,  $J$  = 1.9, 8.1 Hz, 1H), 8.08 (d,  $J$   
26 = 1.9 Hz, 1H), 8.11 (d,  $J$  = 8.7 Hz, 2H).

27 4-[(5,5-Dimethyl-8(7H)-(propyliden-2-yl)-5,6-dihydronaphthalen-  
28 2-yl)]carbonyl}oxy]benzoic acid (Compound E14)

To a solution of 2-trimethylsilylethyl 4-[(5,5-dimethyl-5,6-dihydro-8(7H)-(propyliden-2-yl)-2-naphthalenyl)carbonyl]oxy]benzoate (Compound E13, 84.0 mg, 0.181 mmol) in 2.0 mL THF at 0 °C was added 130.7 mg of tetrabutylammonium fluoride (0.50 mmol; 0.5 mL of a 1M solution in THF). After stirring at 0 °C for 1.5 h and at room temperature for 4.5 h, the reaction was diluted with EtOAc and washed with H<sub>2</sub>O and saturated aqueous NaCl before being dried over MgSO<sub>4</sub>. The solvents were removed under reduced pressure and the residue crystalized from CH<sub>3</sub>CN to give the product as a colorless solid.

<sup>1</sup>H NMR(acetone-d<sub>6</sub>): δ 1.29 (s, 6H), 1.67 (t, J = 6.9 Hz, 2H), 1.87 (s, 3H), 1.99 (s, 3H), 2.56 (t, J = 6.9 Hz, 2H), 7.43 (d, J = 8.6 Hz, 2H), 7.54 (d, J = 8.2 Hz, 1H), 7.97 (dd, J = 1.9, 8.2 Hz, 1H), 8.06 (d, J = 1.9 Hz, 1H), 8.14 (d, J = 8.7 Hz, 2H).

Ethyl 4-[(5,5-dimethyl-8(7H)-(propyliden-2-yl)-5,6-dihydronaphthalen-2-yl)carbonyl]oxy]benzoate (Compound E15)

A solution of 5,5-dimethyl-5,6-dihydro-8(7H)-(propyliden-2-yl)-2-naphthalenecarboxylic acid (Compound E12, 31.0 mg, 0.127 mmol), ethyl 4-hydroxybenzoate (27.4 mg, 0.165 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (31.6 mg, 0.165 mmol), and 4-*N,N*-dimethylaminopyridine (20.2 mg, 0.165 mmol) in 2.0 mL DMF was stirred overnight at room temperature. EtOAc (50 mL) was added and the solution washed with H<sub>2</sub>O, 5% HCl, saturated aqueous NaCO<sub>3</sub>, and saturated aqueous NaCl before being dried over MgSO<sub>4</sub>. Removal of the solvents under reduced pressure and column chromatography (5% EtOAc-hexanes) of the residual oil afforded the title compound as a colorless oil.

<sup>1</sup>H NMR(CDCl<sub>3</sub>) : δ 1.28 (s, 6H), 1.41 (t, J = 7.1 Hz, 2H), 1.66 (t, J = 6.9 Hz, 2H), 1.86 (s, 3H), 2.00 (s, 3H), 2.56 (t, J = 6.9 Hz, 2H), 4.40 (q, J = 7.1 Hz, 2H), 7.29 (d, J = 8.7 Hz, 2H), 7.43 (d, J = 8.1 Hz, 1H), 7.98 (dd, J = 1.8, 8.1 Hz, 1H), 8.09 (d, J = 1.8 Hz, 1H), 8.12 (d, J = 8.7 Hz, 2H).

Ethyl 4-[(5,5-dimethyl-8(7H)-(propyliden-2-yl)-5,6-dihydronaphthalen-2-yl)]carboxamido]benzoate (Compound E16)

A solution of 1(2H)-(propyliden-2-yl)-3,4-dihydro-4,4-dimethylnaphthalene-7-carboxylic acid (Compound E12, 100.0 mg, 0.410 mmol), ethyl 4-aminobenzoate (81.0 mg, 0.490 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (117.0 mg, 0.615 mmol), and 4-*N,N*-dimethylaminopyridine (61.0 mg, 0.500 mmol) in 3.0 mL DMF was stirred overnight at room temperature. EtOAc (100 mL) was added and the solution washed with H<sub>2</sub>O, 10% HCl, saturated aqueous NaCO<sub>3</sub>, and saturated aqueous NaCl before being dried over MgSO<sub>4</sub>. Removal of the solvents under reduced pressure and column chromatography (10-15% EtOAc-hexanes) of the residual oil afforded the title compound as a colorless solid.

<sup>1</sup>H NMR(CDCl<sub>3</sub>) : δ 1.29 (s, 6H), 1.40 (t, J = 7.1 Hz, 2H), 1.64 (t, J = 7.0 Hz, 2H), 1.86 (s, 3H), 2.00 (s, 3H), 2.52 (t, J = 6.6 Hz, 2H), 4.37 (q, J = 7.1 Hz, 2H), 7.60 (d, J = 8.1 Hz, 1H), 7.63 (dd, J = 1.8, 8.1 Hz, 1H), 7.73 (d, J = 8.6 Hz, 2H), 7.75 (d, J = 1.8 Hz, 1H), 7.92 (s, 1H), 8.06 (d, J = 8.6 Hz, 2H).

4-[(5,5-Dimethyl-8(7H)-(propyliden-2-yl)-5,6-dihydronaphthalen-2-yl)]carboxamido]benzoic acid (Compound E17)

To a solution of ethyl 4-[(5,5-dimethyl-8(7H)-(propyliden-2-yl)-5,6-dihydronaphthalen-2-yl)]carboxamido]benzoate

(Compound E16, 25.0 mg, 0.064 mmol) in 3.0 mL of EtOH and 3.0 mL THF was added NaOH (80.0 mg, 2.00 mmol; 2.0 mL of a 1N aqueous solution). After stirring overnight at room temperature the reaction was quenched by the addition of 10% aqueous HCl. The mixture was extracted with EtOAc and the combined organic layers were washed with H<sub>2</sub>O and saturated aqueous NaCl and thereafter dried over Na<sub>2</sub>SO<sub>4</sub>. Removal of the solvents under pressure and crystallization from CH<sub>3</sub>CN afforded the title compound as a colorless solid.

<sup>1</sup>H NMR(acetone-d<sub>6</sub>): δ 1.25 (s, 6H), 1.64 (t, J = 6.9 Hz, 2H), 1.85 (s, 3H), 1.96 (s, 3H), 2.55 (t, J = 6.9 Hz, 2H), 7.45 (d, J = 8.1 Hz, 1H), 7.78 (dd, J = 1.9, 8.1 Hz, 1H), 7.88 (d, J = 1.9 Hz, 1H), 7.95-8.05 (m, 4H), 9.71 (s, 1H).

Methyl-5,5-dimethyl-5,6-dihydro-8-(phenylthio)-naphthalene-2-carboxylate (Compound E18)

To a solution of methyl-5,5-dimethyl-5,6-dihydro-naphthalen-8(7H)-one-2-carboxylate (Compound E2, 835.0 mg, 3.60 mmol) in 25.0 mL of THF at room temperature was added TiCl<sub>4</sub> (670.0 mg, 3.55 mmol). Thereafter a solution of thiophenol (430.0 mg, 3.90 mmol) and Et<sub>3</sub>N (730.0 mg, 7.20 mmol) in 10 mL THF was added. The resulting brown mixture was stirred for 6 h before H<sub>2</sub>O was carefully added to quench the reaction. The product was extracted into Et<sub>2</sub>O and the combined organic layers washed with saturated aqueous NaCl and dried over MgSO<sub>4</sub>. Removal of the solvents under reduced pressure afforded a solid from which the title compound was isolated as a yellow solid by column chromatography (5% EtOAc-hexanes).

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.34 (s, 6H), 2.40 (d, J = 4.7 Hz, 2H), 3.85 (s,

1 3H), 6.51 (t, J = 4.7 Hz, 1H), 7.10-7.36 (m, 5H), 7.38 (d, J = 8.1 Hz,  
2 1H), 7.88 (dd, J = 1.8, 8.0 Hz, 1H), 8.30 (d, J = 1.8 Hz, 1H).

3 5,5-Dimethyl-5,6-dihydro-8-(phenylthio)-naphthalene-2-carboxylic  
4 acid (Compound E19)

5 To a solution of methyl 5,5-dimethyl-5,6-dihydro-8-  
6 (phenylthio)-naphthalene-2-carboxylate (Compound E18, 300.0  
7 mg, 0.926 mmol) in 4.0 mL of EtOH and 2.0 mL THF was added  
8 NaOH (200.0 mg, 5.00 mmol; 5.0 mL of a 1N aqueous solution).  
9 After stirring overnight at room temperature the reaction was  
10 quenched by the addition of 10% aqueous HCl. The mixture was  
11 extracted with EtOAc and the combined organic layers washed  
12 with H<sub>2</sub>O and saturated aqueous NaCl before being dried over  
13 Na<sub>2</sub>SO<sub>4</sub>. Removal of the solvents under pressure afforded the  
14 title compound as a yellow solid.

15 <sup>1</sup>H NMR(CDCl<sub>3</sub>): δ 1.35 (s, 6H), 2.41 (d, J = 4.6 Hz, 2H), 6.54  
16 (t, J = 4.6 Hz, 1H), 7.10-7.34 (m, 5H), 7.40 (d, J = 8.1 Hz, 1H),  
17 7.92 (dd, J = 1.8, 8.1 Hz), 8.36 (d, J = 1.8 Hz, 1H).

18 Ethyl 4-[(5,5-dimethyl-8-(phenylthio)-5,6-dihydronaphthalen-2-  
19 yl)]carboxamido]benzoate (Compound E20)

20 A solution of 5,5-dimethyl-5,6-dihydro-8-(phenylthio)-  
21 naphthalene-2-carboxylic acid (Compound E19, 183.0 mg, 0.580  
22 mmol), ethyl 4-aminobenzoate (107.0 mg, 0.650 mmol), 1-(3-  
23 dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (144.0  
24 mg, 0.750 mmol), and 4-dimethylaminopyridine (85.0 mg, 0.700  
25 mmol) in 5.0 mL DMF was stirred overnight at room temperature.  
26 EtOAc (100 mL) was added and the solution washed with H<sub>2</sub>O  
27 and saturated aqueous NaCl before being dried over MgSO<sub>4</sub>.  
28 Removal of the solvents under reduced pressure and column

1 chromatography (20% EtOAc-hexanes) of the residual oil  
2 afforded the title compound as a colorless solid.

3  $^1\text{H}$  NMR( $\text{CDCl}_3$ ) :  $\delta$  1.37 (s, 6H), 1.40 (t,  $J = 7.1$  Hz, 3H), 2.45  
4 (d,  $J = 4.7$  Hz, 2H), 4.37 (q,  $J = 7.1$  Hz, 2H), 6.65 (t,  $J = 4.7$  Hz,  
5 1H), 7.17-7.35 (m, 5H), 7.45 (d,  $J = 8.1$  Hz, 1H), 7.52 (s, 1H),  
6 7.60 (d,  $J = 8.7$  Hz, 2H), 7.77 (dd,  $J = 1.8, 8.1$  Hz, 1H), 7.96 (d,  $J$   
7  $= 2.0$  Hz, 1H), 8.03 (d,  $J = 8.7$  Hz, 2H).

8 4-[(5,5-Dimethyl-8-(phenylthio)-5,6-dihydronaphthalen-2-  
9 yl)carboxamido]benzoic acid (Compound E21)

10 To a solution of ethyl 4-[(5,5-dimethyl-8-(phenylthio)-5,6-  
11 dihydronaphthalen-2-yl)carboxamido]benzoate (Compound E20,  
12 90.0 mg, 0.196 mmol) in 3.0 mL of EtOH and 3.0 mL THF was  
13 added NaOH (120.0 mg, 3.00 mmol; 3.0 mL of a 1N aqueous  
14 solution). After stirring overnight at room temperature the  
15 reaction was quenched by the addition of 10% aqueous HCl. The  
16 mixture was extracted with EtOAc and the combined organic  
17 layers washed with  $\text{H}_2\text{O}$  and saturated aqueous NaCl before being  
18 dried over  $\text{Na}_2\text{SO}_4$ . Removal of the solvents under pressure  
19 afforded the title compound as a pale yellow solid.

20  $^1\text{H}$  NMR(acetone- $d_6$ ):  $\delta$  1.36 (s, 6H), 2.46 (d,  $J = 4.7$  Hz, 2H),  
21 6.11 (t,  $J = 4.7$  Hz, 1H), 7.13-7.36 (m, 5H), 7.51 (d,  $J = 8.0$  Hz,  
22 1H), 7.85 (dd,  $J = 1.9, 8.0$  Hz, 1H), 7.91-8.03 (m, 4H), 8.24 (d,  $J$   
23  $= 1.9$  Hz, 1H), 9.67 (s, 1H).

24 4-[(5,5-Dimethyl-8-(phenylsulfonyl)-5,6-dihydronaphthalen-2-  
25 yl)carboxamido]benzoic acid (Compound E22)

26 To a solution of 4-[(5,5-dimethyl-8-(phenylsulfonyl)-5,6-  
27 dihydronaphthalen-2-yl)carboxamido]benzoic acid (Compound  
28 E21, 60.0 mg, 0.140 mmol) in 6.0 mL  $\text{Et}_2\text{O}$ , 3.0 mL  $\text{CH}_2\text{Cl}_2$ , and



1 2.0 mL THF at 0 °C was added *m*-chloroperbenzoic acid (57-  
 2 80%) (74-110 mg, 0.430-0.640 mmol). The resulting solution was  
 3 warmed to room temperature and stirred overnight. Water was  
 4 added and the mixture extracted with EtOAc. The combined  
 5 organic layers were washed with H<sub>2</sub>O and saturated aqueous NaCl  
 6 before being dried over Na<sub>2</sub>SO<sub>4</sub>. Removal of the solvents under  
 7 reduced pressure and crystallization of the residue from CH<sub>3</sub>CN  
 8 afforded the title compound as a colorless solid.

9 <sup>1</sup>H NMR (acetone-d<sub>6</sub>): δ 1.23 (s, 6H), 2.60 (d, J = 4.9 Hz, 2H),  
 10 7.51-7.62 (m, 5H), 7.89 (dd, J = 1.8, 7.9 Hz, 1H), 7.94 (s, 1H),  
 11 7.95-8.06 (m, 6H), 8.61 (d, J = 1.9 Hz, 1H).

12 Ethyl 4-[(5,5-dimethyl-8-(phenylthio)-5,6-dihydronaphthalen-2-  
 13 yl)]carbonyloxybenzoate (Compound E23)

14 A solution of 5,5-dimethyl-5,6-dihydro-8-(phenylthio)-  
 15 naphthalene-2-carboxylic acid (Compound E19, 150.0 mg, 0.484  
 16 mmol), ethyl 4-hydroxybenzoate (88.5 mg, 0.530 mmol), 1-(3-  
 17 dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (120.6  
 18 mg, 0.630 mmol), and 4-*N,N*-dimethylaminopyridine (77.0 mg,  
 19 0.630 mmol) in 5.0 mL DMF was stirred overnight at room  
 20 temperature. EtOAc (50 mL) was added and the solution washed  
 21 with H<sub>2</sub>O and saturated aqueous NaCl before being dried over  
 22 MgSO<sub>4</sub>. Removal of the solvents under reduced pressure and  
 23 column chromatography (10-15% EtOAc-hexanes) of the residual  
 24 oil afforded the title compound as a colorless solid.  
 25 <sup>1</sup>H NMR(CDCl<sub>3</sub>): δ 1.37(s, 6H), 1.40 (t, J = 7.1 Hz, 3H), 2.44 (d,  
 26 J = 4.8 Hz, 2H), 4.39 (q, J = 7.1 Hz, 2H), 6.57 (t, J = 4.8 Hz,  
 27 1H), 7.15-7.36 (m, 7H), 7.45 (d, J = 8.1 Hz, 1H), 8.01 (dd, J =  
 28 1.8, 81.Hz, 1H), 8.10 (d, J = 8.7 Hz, 2H), 8.44 (d, J = 1.8 Hz,

1 1H).

2 Ethyl 4-[(5,5-dimethyl-8-(phenylsulfonyl)-5,6-dihydronaphthalen-  
3 2-yl)]carbonyl]oxy]benzoate (Compound E24)

4 A solution of ethyl 4-[(5,5-dimethyl-8-(phenylthio)-5,6-  
5 dihydronaphthalen-2-yl)]carbonyl]oxy]benzoate (Compound E23,  
6 50.0 mg, 0.109 mmol) in 5.0 mL Et<sub>2</sub>O at 0 °C was added *m*-  
7 chloroperbenzoic acid (50%) (25 mg, 0.145 mmol). The resulting  
8 solution was warmed to room temperature and stirred overnight.  
9 Et<sub>2</sub>O was added and the organic layer washed with H<sub>2</sub>O,  
10 saturated aqueous NaHCO<sub>3</sub>, and saturated aqueous NaCl before  
11 being dried over Na<sub>2</sub>SO<sub>4</sub>. Removal of the solvents under reduced  
12 pressure and column chromatography (20% EtOAc-hexanes)  
13 afforded the title compound as a colorless solid.

14 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.27 (s, 6H), 1.42 (t, J = 7.1 Hz, 3H), 2.56  
15 (d, J = 4.9 Hz, 2H), 4.40 (q, J = 7.1 Hz, 2H), 7.27 (d, J = 8.7 Hz,  
16 2H), 7.43-7.57 (m, 5H), 8.02 (m, 3H), 8.14 (d, J = 8.7 Hz, 2H),  
17 8.68 (d, J = 1.7 Hz, 1H).

18 2-(Trimethylsilyl)ethyl 4-[(5,5-dimethyl-8-(phenylthio)-5,6-  
19 dihydronaphthalen-2-yl)]carbonyl]oxy]benzoate (Compound E25)

20 A solution of 5,5-dimethyl-5,6-dihydro-8-(phenylthio)-  
21 naphthalene-2-carboxylic acid (Compound E19, 170.0 mg, 0.548  
22 mmol), 2-trimethylsilylethyl 4-hydroxybenzoate (130.0 mg, 0.548  
23 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide  
24 hydrochloride (126.0 mg, 0.657 mmol), and 4-*N,N*-  
25 dimethylaminopyridine (74.0 mg, 0.600 mmol) in 4.0 mL DMF was  
26 stirred overnight at room temperature. EtOAc (100 mL) was  
27 added and the solution washed with H<sub>2</sub>O, 10% HCl, and  
28 saturated aqueous NaCl before being dried over MgSO<sub>4</sub>.

1 Removal of the solvents under reduced pressure and column  
2 chromatography (5% EtOAc-hexanes) of the residual oil afforded  
3 the title compound as a colorless oil.

4  $^1\text{H}$  NMR( $\text{CDCl}_3$ ):  $\delta$  0.10 (s, 9H), 1.15 (t,  $J$  = 8.4 Hz, 2H), 1.38 (s,  
5 6H), 2.44 (d,  $J$  = 4.7 Hz, 2H), 4.43 (d,  $J$  = 8.4 Hz, 2H), 6.58 (t,  $J$   
6 = 4.7 Hz, 1H), 7.16-7.36 (m, 7H), 7.45 (d,  $J$  = 8.1 Hz, 1H), 8.02  
7 (dd,  $J$  = 1.8, 8.1 Hz, 1H), 8.10 (d,  $J$  = 8.7 Hz, 2H), 8.45 (d,  $J$  =  
8 1.8 Hz, 1H).

9 4-[(5,5-Dimethyl-8-(phenylthio)-5,6-dihydronaphthalen-2-  
10 yl)]carbonyloxy]benzoic acid (Compound E26)

11 To a solution of 2-(trimethylsilyl)ethyl 4-[(5,5-dimethyl-5,6-  
12 dihydro-8-(phenylthio)-naphthalen-2-yl)carbonyloxy]-benzoate  
13 (Compound E25, 200.0 mg, 0.377 mmol) in 2.0 mL THF at 0 °C  
14 was added tetrabutylammonium fluoride (295.5 mg, 1.13 mmol;  
15 1.13 mL of a 1M solution in THF). After 2 h the solution was  
16 warmed to room temperature and stirred overnight. EtOAc was  
17 added and the organic layer washed with  $\text{H}_2\text{O}$  and saturated  
18 aqueous NaCl. Removal of the solvents under reduced pressure  
19 and recrystallization of the residue from  $\text{CH}_3\text{CN}$  afforded the title  
20 compound as a pale yellow solid.

21  $^1\text{H}$  NMR(acetone- $d_6$ ):  $\delta$  1.39 (s, 6H), 2.51 (d,  $J$  = 4.7 Hz, 2H),  
22 6.67 (t,  $J$  = 4.7 Hz, 1H), 7.19-7.38 (m, 6H), 7.61 (d,  $J$  = 8.1 Hz,  
23 1H), 8.02 (dd,  $J$  = 1.8, 8.1 Hz, 1H), 8.12 (d,  $J$  = 8.6 Hz, 1H), 8.43  
24 (d,  $J$  = 8.1 Hz, 1H).

25 4-[(5,5-Dimethyl-8-(phenylsulfonyl)-5,6-dihydronaphthalen-2-  
26 yl)]carbonyloxy]benzoic acid (Compound E27)

27 To a solution of 4-[(5,5-dimethyl-5,6-dihydro-8-  
28 (phenylthio)-naphthalen-2-yl)carbonyloxy]-benzoic acid

1 (Compound E26, 50.0 mg, 0.116 mmol) in 3.0 mL  $\text{CH}_2\text{Cl}_2$ , and  
 2 1.0 mL THF at 0 °C was added *m*-chloroperbenzoic acid (57-  
 3 80%) (34.52 mg, 0.197-0.299 mmol). The resulting solution was  
 4 warmed to room temperature and stirred overnight. Water was  
 5 added and the mixture extracted with EtOAc. The combined  
 6 organic layers were washed with  $\text{H}_2\text{O}$  and saturated aqueous NaCl  
 7 before being dried over  $\text{Na}_2\text{SO}_4$ . Removal of the solvents under  
 8 reduced pressure and crystallization of the residue from  $\text{CH}_3\text{CN}$   
 9 afforded the title compound as a colorless solid.

10  $^1\text{H}$  NMR (acetone- $d_6$ ):  $\delta$  1.27 (s, 6H), 2.65 (d,  $J$  = 4.8 Hz, 2H),  
 11 7.14 (d,  $J$  = 8.7 Hz, 2H), 7.57-7.68 (m, 5H), 8.03 (m, 3H), 8.17 (d,  
 12  $J$  = 8.7 Hz, 2H), 8.77 (d,  $J$  = 1.8 Hz, 1H).

13 Ethyl 4-[(5,5-Dimethyl-8(7H)-one-5,6-dihydronaphthalen-2-  
 14 yl)carboxamido]benzoate (Compound E28)

15 To a solution of 5,5-dimethyl-5,6-dihydro-8(7H)-one-  
 16 naphthalene-2-carboxylic acid (Compound E3, 400.0 mg, 1.833  
 17 mmol), ethyl 4-aminobenzoate (317.8 mg, 1.924 mmol), 1-(3-  
 18 dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (386.5  
 19 mg, 2.016 mmol), and 4-dimethylaminopyridine (246.3 mg, 2.016  
 20 mmol) in 18.0 mL  $\text{CH}_2\text{Cl}_2$  was stirred at room temperature for  
 21 2h. EtOAc (25 mL) was added and the solution washed with  
 22  $\text{H}_2\text{O}$ , 1M HCl, and saturated aqueous NaCl before being dried  
 23 over  $\text{MgSO}_4$ . Removal of the solvents under reduced pressure  
 24 and column chromatography (30% EtOAc-hexanes) of the residue  
 25 afforded the title compound as a colorless solid.

26  $^1\text{H}$  NMR( $\text{CDCl}_3$ ):  $\delta$  1.41 (t,  $J$  = 7.1 Hz, 3H), 1.45 (s, 6H), 2.08 (t,  
 27  $J$  = 7.1 Hz, 2H), 2.80 (t,  $J$  = 6.6 Hz, 2H), 4.38 (q,  $J$  = 7.2 Hz,  
 28 2H), 7.62 (d,  $J$  = 8.3 Hz, 1H), 7.78 (d,  $J$  = 8.7 Hz, 2H), 8.09 (d,  $J$

1 = 8.6 Hz, 2H), 8.14 (bs, 1H), 8.21 (dd,  $J = 2.1, 8.3$  Hz, 1H), 8.42  
 2 (d,  $J = 2.1$  Hz, 1H).

3 4-[(5,5-Dimethyl-8(7H)-one-5,6-dihydronaphthalen-2-  
 4 yl)carboxamido]benzoic acid (Compound E29)

5 A solution of ethyl 4-[(5,5-dimethyl-8(7H)-one-5,6-  
 6 dihydronaphthalen-2-yl)carboxamido]benzoate (Compound E28,  
 7 50.0 mg, 0.137 mmol) and NaOH (54.7 mg, 1.37 mmol; 0.68 mL of  
 8 a 2N aqueous solution) in 2.0 mL EtOH and 1.0 mL THF was  
 9 stirred at room temperature overnight. The reaction mixture was  
 10 acidified with 10% HCl and extracted with EtOAc. The combined  
 11 organic layers were washed with H<sub>2</sub>O and saturated aqueous NaCl  
 12 before being dried over Na<sub>2</sub>SO<sub>4</sub>. Removal of the solvents under  
 13 reduced pressure and crystallization of the residual solid from  
 14 MeOH/H<sub>2</sub>O afforded the title compound as yellow crystals.  
 15 <sup>1</sup>H NMR (DMSO-d<sub>6</sub>):  $\delta$  1.40 (s, 6H), 2.01 (t,  $J = 6.7$  Hz, 2H),  
 16 2.74 (t,  $J = 7.0$  Hz, 2H), 7.74 (d,  $J = 8.4$  Hz, 1H), 7.93 (m, 4H),  
 17 8.16 (dd,  $J = 2.1, 8.3$  Hz, 1H), 8.45 (d,  $J = 2.0$  Hz, 1H), 10.68 (s,  
 18 1H), 12.75 (bs, 1H).

19 Ethyl 4-[(5,5-dimethyl-8(7H)-anti-(O-methyloxime)-5,6-  
 20 dihydronaphthalen-2-yl)carboxamido]benzoate (Compound E30)

21 A mixture of ethyl 4-[(5,5-dimethyl-5,6-dihydro-8(7H)-one-  
 22 naphthalen-2-yl)carboxamido]-benzoate (Compound E28, 100.0  
 23 mg, 0.274 mmol), O-methylhydroxylamine hydrochloride (25.1 mg,  
 24 0.301 mmol), and NaOAc)3H<sub>2</sub>O (81.9 mg, 0.602 mmol) in 3.0 mL  
 25 of EtOH was heated to 65 °C for 3 h and then stirred at room  
 26 temperature for 68 h. The reaction was diluted with H<sub>2</sub>O and  
 27 extracted with EtOAc. The combined organic layers were washed  
 28 with H<sub>2</sub>O and saturated aqueous NaCl before being dried over

1  $\text{MgSO}_4$ . Removal of the solvents under reduced pressure and  
 2 column chromatography (20-30% EtOAc-hexanes) of the residue  
 3 afforded the title compound as a colorless solid.

4  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.32 (s, 6H), 1.40 (t,  $J = 7.2$  Hz, 2H), 1.75  
 5 (t,  $J = 7.0$  Hz, 2H), 2.81 (t,  $J = 7.0$  Hz, 2H), 4.04 (s, 3H), 4.37 (q,  
 6  $J = 7.1$  Hz, 2H), 7.49 (d,  $J = 8.2$  Hz, 1H), 7.76 (dd,  $J = 1.9, 8.7$   
 7 Hz, 2H), 7.88 (dd,  $J = 2.1, 8.3$  Hz, 1H), 8.06 (dd,  $J = 1.7, 8.7$  Hz,  
 8 2H), 8.12 (bs, 1H), 8.40 (d,  $J = 2.0$  Hz, 1H).

9 4-[(5,5-Dimethyl-8(7H)-anti-(O-methyloxime)-5,6-  
 10 dihydronaphthalen-2-yl)carboxamido]benzoic acid (Compound  
 11 E31)

12 A solution of ethyl (E)-4-[[[(5,5-dimethyl-5,6-dihydro-8(7H)-  
 13 anti-(O-methyloxime)-naphthalen-2-yl)carboxamido]-benzoate  
 14 (Compound E30, 31.4 mg, 0.080 mmol) and NaOH (31.8 mg,  
 15 0.796 mmol; 0.40 mL of a 2N aqueous solution) in 2 mL EtOH  
 16 was stirred at room temperature overnight. The reaction was  
 17 acidified with 10% HCL and extracted with EtOAc. The  
 18 combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated  
 19 under reduced pressure to give an off-white solid. Crystallization  
 20 from  $\text{Et}_2\text{O}$  afforded the title compound as a colorless solid.

21  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  1.27 (s, 6H), 1.69 (t,  $J = 6.9$  Hz, 2H),  
 22 2.74 (t,  $J = 6.9$  Hz, 2H), 3.96 (s, 3H), 7.58 (d,  $J = 8.3$  Hz, 1H),  
 23 7.90 (m, 5H), 8.36 (d,  $J = 2.0$  Hz, 1H), 10.57 (s, 1H), 12.73 (bs,  
 24 1H).

25 (+/-) Ethyl 4-[(5,5-dimethyl-8-hydroxy-5,6,7,8-  
 26 tetrahydronaphthalen-2-yl)carboxamido]benzoate (Compound E32)

27 A solution of ethyl 4-[(5,5-dimethyl-5,6-dihydro-8(7H)-one-  
 28 naphthalen-2-yl)carboxamido]-benzoate (Compound E28, 125.0

1 mg, 0.342 mmol) in 2.0 mL EtOH and 2.0 mL THF was cooled to  
 2 0° C and treated with NaBH<sub>4</sub> (11.5 mg, 0.304 mmol). After 4 h  
 3 the reaction was quenched by the careful addition of H<sub>2</sub>O,  
 4 followed by 0.5 mL 1M HCl. EtOAc (25 mL) was added and the  
 5 solution washed with 1M HCl, dilute aqueous NaHCO<sub>3</sub>, H<sub>2</sub>O and  
 6 saturated aqueous NaCl before being dried over Na<sub>2</sub>SO<sub>4</sub>.  
 7 Removal of the solvents under reduced pressure afforded the title  
 8 compound as a colorless solid.

9 <sup>1</sup>H NMR (acetone-d<sub>6</sub>): δ 1.28 (s, 3H), 1.31 (s, 3H), 1.35 (t, J =  
 10 7.2 Hz, 3H), 1.65 (m, 1H), 1.88 (m, 3H), 4.32 (q, J = 7.1 Hz, 2H),  
 11 4.69 (q, J = 5.8 Hz, 1H), 7.49 (d, J = 8.2 Hz, 1H), 7.83 (dd, J =  
 12 2.2, 8.3 Hz, 1H), 7.99 (s, 4H), 8.09 (d, J = 1.9 Hz, 1H), 9.81 (bs,  
 13 1H).

14 (+/-) 4-[(5,5-Dimethyl-8-hydroxy-5,6,7,8-tetrahydronaphthalen-2-  
 15 yl)carboxamido]benzoic acid (Compound E33)

16 A mixture of (+/-) ethyl 4-[(5,5-dimethyl-5,6,7,8-tetrahydro-  
 17 8-hydroxy-naphthalen-2-yl)carboxamido]-benzoate (Compound  
 18 E32, 50.0 mg, 0.136 mmol) and NaOH (54.4 mg, 1.36 mmol; 0.68  
 19 mL of a 2N aqueous solution) in 3 mL EtOH was stirred at room  
 20 temperature for 19h. The resulting solution was acidified with  
 21 10% HCl and extracted with EtOAc. The combined organic  
 22 layers were washed with H<sub>2</sub>O and saturated aqueous NaCl, and  
 23 then dried over Na<sub>2</sub>SO<sub>4</sub>. Removal of the solvents under reduced  
 24 pressure afforded the title compound as a colorless solid.  
 25 <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 1.25 (s, 3H), 1.28 (s, 3H), 1.61 (m, 1H),  
 26 1.80 (m, 2H), 1.95 (m, 1H), 4.87 (m, 1H), 5.30 (bs, 1H), 7.49 (d, J  
 27 = 8.2 Hz, 1H), 7.78 (dd, J = 1.9, 8.2 Hz, 1H), 7.49 (s, 4H), 8.01  
 28 (s, 1H), 10.47 (s, 1H), 12.72 (bs, 1H).

1 (+/-) Ethyl 4-[(5,5-dimethyl-8-(O-methoxymethyl)-5,6,7,8-  
 2 tetrahydronaphthalen-2-yl)carboxamido]benzoate (Compound E34)

3 To a solution of (+/-) ethyl 4-[(5,5-dimethyl-8-hydroxy-  
 4 5,6,7,8-tetrahydronaphthalen-2-yl)carboxamido]benzoate  
 5 (Compound E32, 57.0 mg, 0.155 mmol) in 5.0 mL CH<sub>2</sub>Cl<sub>2</sub> at 0 °C  
 6 was added diisopropylethyl amine (276.2 mg, 2.137 mmol),  
 7 chloromethyl methyl ether (37.7 mg, 0.469 mmol), and a catalytic  
 8 amount of tetrabutylammonium iodide. The resulting solution was  
 9 stirred at 45 °C overnight. Upon cooling to room temperature  
 10 the solution was diluted with EtOAc and washed with 5% HCl,  
 11 H<sub>2</sub>O, saturated aqueous NaHCO<sub>3</sub>, and saturated aqueous NaCl,  
 12 before being dried over MgSO<sub>4</sub>. Removal of the solvents under  
 13 reduced pressure, followed by column chromatography (15%  
 14 EtOAc-hexanes) afforded the title compound as a colorless oil.  
 15 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.27 (s, 3H), 1.35 (s, 3H), 1.39 (t, J = 7.1  
 16 Hz, 3H), 1.64 (m, 1H), 1.90-2.13 (m, 3H), 3.48 (s, 3H), 4.36 (q, J  
 17 = 7.1 Hz, 2H), 4.67 (t, J = 5.0 Hz, 1H), 4.79 (d, J = 6.9 Hz, 1H),  
 18 4.89 (d, J = 6.9 Hz, 1H), 7.43 (d, J = 8.2 Hz, 1H), 7.74 (m, 3H),  
 19 7.88 (d, J = 2.0 Hz, 1H), 8.03 (d, J = 8.7 Hz, 2H), 8.18 (s, 1H).

20 (+/-) 4-[(5,5-Dimethyl-8-(O-methoxymethyl)-5,6,7,8-  
 21 tetrahydronaphthalen-2-yl)carboxamido]benzoic acid (Compound  
 22 E35)

23 A mixture of (+/-) ethyl 4-[(5,5-dimethyl-8-(O-  
 24 methoxymethyl)-5,6,7,8-tetrahydronaphthalen-2-  
 25 yl)carboxamido]benzoate (Compound E34, 30.0 mg, 0.073 mmol)  
 26 and NaOH (40.0 mg, 1.00 mmol; 1.0 mL of a 1N aqueous  
 27 solution) in 1.0 mL EtOH and 1.0 mL THF was stirred at room  
 28 temperature overnight. The resulting solution was acidified with



1 10% HCl and extracted with EtOAc. The combined organic  
 2 layers were washed with H<sub>2</sub>O and saturated aqueous NaCl, and  
 3 then dried over Na<sub>2</sub>SO<sub>4</sub>. Removal of the solvents under reduced  
 4 pressure afforded the title compound as a colorless oil.

5 <sup>1</sup>H NMR (acetone-d<sub>6</sub>): δ 1.27 (s, 3H), 1.34 (s, 3H), 1.65 (m, 1H),  
 6 1.95 (m, 2H), 2.08 (m, 1H), 3.42 (s, 3H), 4.66 (t, J = 5.0 Hz, 1H),  
 7 4.77 (d, J = 6.9 Hz, 1H), 4.84 (d, J = 6.9 Hz, 1H), 7.53 (d, J = 8.2  
 8 Hz, 1H), 7.86 (dd, J = 2.0, 8.2 Hz, 1H), 8.00 (m, 5H), 9.78 (s,  
 9 1H).

10 2-(Trimethylsilyl)ethyl 4-[(5,5-dimethyl-8(7H)-one-5,6-  
 11 dihydronaphthalen-2-yl)carbonyl]oxy]benzoate (Compound E36)

12 To a solution of 5,5-dimethyl-5,6-dihydro-8(7H)-one-  
 13 naphthalene-2-carboxylic acid (Compound E3, 154.0 mg, 0.706  
 14 mmol), 2-(trimethylsilyl)ethyl 4-hydroxybenzoate (185.0 mg, 0.777  
 15 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide  
 16 hydrochloride (176.0 mg, 0.918 mmol), and 4-  
 17 dimethylaminopyridine (112.2 mg, 0.918 mmol) in 4.0 mL DMF  
 18 was stirred at room temperature overnight. EtOAc (100 mL) was  
 19 added and the solution washed with H<sub>2</sub>O, 1M HCl, saturated  
 20 aqueous NaHCO<sub>3</sub>, and saturated aqueous NaCl before being  
 21 dried over MgSO<sub>4</sub>. Removal of the solvents under reduced  
 22 pressure and column chromatography (10% EtOAc-hexanes) of  
 23 the residue afforded the title compound as a colorless solid.  
 24 <sup>1</sup>H NMR(CDCl<sub>3</sub>): δ 0.09 (s, 9H), 1.15 (t, J = 8.3 Hz, 2H), 1.45 (s,  
 25 6H), 2.08 (t, J = 7.0 Hz, 2H), 2.81 (t, J = 7.0 Hz, 2H), 4.43 (t, J  
 26 = 8.3 Hz, 2H), 7.28 (d, J = 8.7 Hz, 2H), 7.60 (d, J = 8.3 Hz, 1H),  
 27 8.12 (d, J = 8.7 Hz, 2H), 8.30 (dd, 1H, J = 1.9, 8.3 Hz, 1H), 8.85  
 28 (d, J = 1.9 Hz, 1H).

1 (+/-)2-Trimethylsilylethyl 4-[[[(5,5-dimethyl-8-hydroxy-5,6,7,8-  
 2 tetrahydronaphthalen-2-yl)carbonyl]oxy]benzoate (Compound E37)

3 A solution of 2-(trimethylsilyl)ethyl 4-[[[(5,5-dimethyl-8(7H)-  
 4 one-5,6-dihydronaphthalen-2-yl)carbonyl]oxy]benzoate  
 5 (Compound E36, 160.0 mg, 0.365 mmol) in 2.0 mL EtOH and 2.0  
 6 mL THF was cooled to 0 °C and treated with NaBH<sub>4</sub> (13.8 mg,  
 7 0.365 mmol). After 3 h the reaction was quenched by the careful  
 8 addition of 5% aqueous HCl. EtOAc (100 mL) was added and  
 9 the solution washed with H<sub>2</sub>O, dilute aqueous NaHCO<sub>3</sub>, and  
 10 saturated aqueous NaCl before being dried over MgSO<sub>4</sub>.

11 Removal of the solvents under reduced pressure followed by  
 12 column chromatography (10-15% EtOAc) afforded the title  
 13 compound.

14 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 0.09 (s, 9H), 1.14 (t, J = 8.4 Hz, 2H), 1.30  
 15 (s, 3H), 1.37 (s, 3H), 1.68 (m, 1H), 1.92 (m, 2H), 2.12 (m, 1H),  
 16 4.45 (t, J = 8.4 Hz, 2H), 4.82 (m, 1H), 7.28 (d, J = 8.7 Hz, 2H),  
 17 7.48 (d, J = 8.3 Hz, 1H), 8.04 (dd, J = 2.0, 8.3 Hz, 1H), 8.11 (d, J  
 18 = 8.7 Hz, 2H), 8.30 (d, J = 2.0 Hz, 1H).

19 (+/-) 2-(Trimethylsilyl)ethyl 4-[[[(5,5-dimethyl-8-(O-  
 20 methoxymethyl)-5,6,7,8-tetrahydronaphthalen-2-  
 21 yl)carbonyl]oxy]benzoate (Compound E38)

22 To a solution of (+/-) 2-trimethylsilylethyl 4-[[[(5,5-  
 23 dimethyl-8-hydroxy-5,6,7,8-tetrahydronaphthalen-2-  
 24 yl)carbonyl]oxy]benzoate (Compound E37, 70.0 mg, 0.159 mmol)  
 25 in 5.0 mL CH<sub>2</sub>Cl<sub>2</sub> at 0 °C were added diisopropylethylamine  
 26 (276.2 mg, 2.137 mmol), and chloromethyl methyl ether (37.7 mg,  
 27 0.469 mmol). The resulting solution was stirred at room  
 28 temperature overnight. The reaction mixture was diluted with

1 EtOAc and washed with 5% HCl, H<sub>2</sub>O, saturated aqueous  
2 NaHCO<sub>3</sub>, and saturated aqueous NaCl, before being dried over  
3 MgSO<sub>4</sub>. Removal of the solvents under reduced pressure,  
4 followed by column chromatography (10% EtOAc-hexanes)  
5 afforded the title compound as a colorless oil.  
6 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 0.09 (s, 9H), 1.14 (t, J = 8.3 Hz, 2H), 1.30 (s,  
7 3H), 1.39 (s, 3H), 1.63 (m, 2H), 1.97 (m, 2H), 3.50 (s, 3H), 4.43 (t,  
8 J = 8.3 Hz, 2H), 4.71 (t, J = 5.0 Hz, 1H), 4.81 (d, J = 7.0 Hz, 1H),  
9 4.91 d, J = 7.0 Hz, 1H), 7.28 (d, J = 8.7 Hz, 2H), 7.49 (d, J = 8.3  
10 Hz, 1H), 8.05 (dd, J = 1.8, 8.3 Hz, 1H), 8.10 (d, J = 8.7 Hz, 2H),  
11 8.19 (d, J = 1.8 Hz, 1H).

12 (+/-) 4-[(5,5-dimethyl-8-(O-methoxymethyl)-5,6,7,8-  
13 tetrahydronaphthalen-2-yl)carbonyl]oxy]benzoic acid (Compound  
14 E39)

15 To a solution of (+/-) 2-trimethylsilylethyl-4-[(5,5-dimethyl-  
16 5,6,7,8-tetrahydro-8-(O-methoxymethyl)naphthalen-2-  
17 yl)carbonyl]oxy]-benzoate (Compound E38, 72.0 mg, 0.148 mmol)  
18 in 2.0 mL THF was added tetrabutylammonium fluoride (130.7  
19 mg, 0.500 mmol; 0.5 mL of a 1M solution in THF). The resulting  
20 solution was stirred overnight at room temperature, diluted with  
21 EtOAc, and washed with H<sub>2</sub>O and saturated aqueous NaCl. The  
22 solution was dried (MgSO<sub>4</sub>) and then concentrated under reduced  
23 pressure. The title compound was isolated as a colorless oil by  
24 preparative TLC (5% MeOH-CH<sub>2</sub>Cl<sub>2</sub>).

25 <sup>1</sup>H MNR (acetone-d<sub>6</sub>): δ 1.30 (s, 3H), 1.37 (s, 3H), 1.67 (m, 1H),  
26 1.95 (m, 2H), 2.11 (m, 1H), 3.42 (s, 3H), 4.70 (t, J = 5.0 Hz, 1H),  
27 4.88 (d, J = 7.0 Hz, 2H), 7.42 (d, J = 8.7 Hz, 2H), 7.62 (d, J =  
28 8.3 Hz, 1H), 7.77 (d, J = 7.0 Hz, 2H), 8.03 (dd, J = 1.9, 8.3 Hz,

1 1H), 8.15 (d, J = 8.7 Hz, 2H), 8.19 d, J = 1.9 Hz, 1H).

2 (+/-) Ethyl 4-[[[(5,5-dimethyl-8-hydroxy-5,6,7,8-  
3 tetrahydronaphthalen-2-yl)carbonyl]oxy]benzoic acid (Compound  
4 E40)

5 A solution of ethyl 4-[[[(5,5-dimethyl-5,6-dihydro-8(7H)-one-  
6 naphthalen-2-yl)carbonyl]oxy]-benzoate (Compound E44, 126.0  
7 mg, 0.344 mmol) in 1.5 mL EtOH and 1.5 mL THF was cooled to  
8 0 °C and treated with NaBH<sub>4</sub> (13.0 mg, 0.344 mmol). After 3 h  
9 the reaction was quenched by the careful addition of H<sub>2</sub>O.

10 EtOAc (50 mL) was added and the solution washed with H<sub>2</sub>O  
11 and saturated aqueous NaCl before being dried over MgSO<sub>4</sub>.

12 Removal of the solvents under reduced pressure followed by  
13 column chromatography (15-20% EtOAc) afforded the title  
14 compound as a colorless oil.

15 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.30 (s, 3H), 1.37 (s, 3H), 1.41 (t, J = 7.1  
16 Hz, 3H), 1.68 (m, 1H), 1.83-1.99 (m, 2H), 2.15 (m, 1H), 4.39 (q, J  
17 = 7.1 Hz, 2H), 4.82 (m, 1H), 7.28 (d, J = 8.7 Hz, 2H), 7.49 (d, J  
18 = 8.3 Hz, 1H), 8.05 (dd, J = 1.8, 8.3 Hz, 1H), 8.12 (d, J = 8.7 Hz,  
19 2H), 8.29 (d, J = 1.8 Hz, 1H).

20 (+/-)Ethyl 4-[[[(5,5-dimethyl-8-(O-methoxymethyl)-5,6,7,8-  
21 tetrahydronaphthalen-2-yl)carbonyl]oxy]benzoate (Compound E41)

22 To a solution of (+/-) ethyl 4-[[[(5,5-dimethyl-5,6,7,8-  
23 tetrahydro-8-hydroxy-naphthalen-2-yl)carbonyl]oxy]-benzoate  
24 (Compound E40, 131.8 mg, 0.358 mmol) in 5.0 mL CH<sub>2</sub>Cl<sub>2</sub> at 0  
25 °C was added diisopropylethylamine (277.5 mg, 2.147 mmol), and  
26 chloromethyl methyl ether (86.9 mg, 1.08 mmol). The resulting  
27 solution was stirred at room temperature overnight. The reaction  
28 mixture was diluted with EtOAc and washed with 10% HCl,

1 H<sub>2</sub>O, saturated aqueous NaHCO<sub>3</sub>, and saturated aqueous NaCl,  
 2 before being dried over MgSO<sub>4</sub>. Removal of the solvents under  
 3 reduced pressure, followed by column chromatography (15%  
 4 EtOAc-hexanes) afforded the title compound as a colorless oil.

5 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.29 (s, 3H), 1.38 (s, 3H), 1.41 (t, J = 7.1 Hz,  
 6 3H), 1.62 (m, 2H), 1.96 (m, 2H), 3.50 (s, 3H), 4.39 (q, J = 7.1 Hz,  
 7 2H), 4.71 (t, J = 5.0 Hz, 1H), 4.80 d, J = 7.0 Hz, 1H), 4.92 (d, J =  
 8 7.0 Hz, 1H), 7.28 (d, J = 8.7 Hz, 2H), 7.49 (d, J = 8.3 Hz, 1H), 8.05  
 9 (dd, J = 1.8, 8.3 Hz, 1H), 8.12 (d, J = 8.7 Hz, 2H), 8.19 (d, J = 1.8  
 10 Hz, 1H).

11 2-(Trimethylsilyl)ethyl-4-[[[(5,5-dimethyl-8(7H)-anti-(O-  
 12 methyloxime)-5,6-dihydronaphthalen-2-yl)carbonyl]oxy]benzoate  
 13 (Compound E42).

14 A mixture of 2-(trimethylsilyl)ethyl 4-[[[(5,5-dimethyl-5,6-  
 15 dihydro-8(7H)-one-naphthalen-2-yl)carbonyl]oxy]-benzoate  
 16 (Compound E36, 80.0 mg, 0.182 mmol), O-methylhydroxylamine  
 17 hydrochloride (22.8 mg, 0.273 mmol), and NaOAc) X 3H<sub>2</sub>O (62.0  
 18 mg, 0.455 mmol) in 3.0 mL of EtOH was stirred at room  
 19 temperature for 5 days. The reaction was diluted with H<sub>2</sub>O and  
 20 extracted with EtOAc. The combined organic layers were washed  
 21 with H<sub>2</sub>O and saturated aqueous NaCl before being dried over  
 22 MgSO<sub>4</sub>. Removal of the solvents under reduced pressure and  
 23 column chromatography (4-8% EtOAc-hexanes) of the residue,  
 24 followed by preparative TLC (20% EtOAc-hexanes, afforded the  
 25 title compound.

26 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 0.09 (s, 9H), 1.14 (t, J = 8.6 Hz, 2H), 1.33  
 27 (s, 6H), 1.76 (t, J = 6.9 Hz, 2H), 2.82 (t, J = 6.9 Hz, 2H), 4.04 (s,  
 28 3H), 4.43 (q, J = 8.4 Hz, 2H), 7.30 (d, J = 8.7 Hz, 2H), 7.49 (d, J

1 = 8.3 Hz, 1H), 8.08 (dd,  $J = 1.9, 8.3$  Hz, 1H), 8.12 (d,  $J = 8.7$  Hz,  
2 2H), 8.78 (d,  $J = 1.9$  Hz, 1H).

3 4-[[[(5,5-dimethyl-8(7H)-anti-(O-methyloxime)-5,6-  
4 dihydronaphthalen-2-yl)carbonyl]oxy]benzoic acid (Compound  
5 E43)

6 To a solution of (trimethylsilyl)ethyl 4-[[[(5,5-dimethyl-  
7 8(7H)-anti-(O-methyloxime)-5,6-dihydronaphthalen-2-  
8 yl)carbonyl]oxy]benzoate (Compound E42, 40.0 mg, 0.086 mmol)  
9 in 1.5 mL THF was added tetrabutylammonium fluoride (68.0 mg,  
10 0.260 mmol; 0.26 mL of a 1M solution in THF). The resulting  
11 solution was stirred for 6 h at room temperature, diluted with  
12 EtOAc, and washed with H<sub>2</sub>O and saturated aqueous NaCl. The  
13 solution was dried (MgSO<sub>4</sub>) and then concentrated under reduced  
14 pressure. The title compound was isolated as a colorless oil by  
15 preparative TLC (5% MeOH-CH<sub>2</sub>Cl<sub>2</sub>).

16 <sup>1</sup>H NMR (acetone-d<sub>6</sub>):  $\delta$  1.34 (s, 6H), 1.78 (t,  $J = 7.0$  Hz, 2H),  
17 2.81 (t,  $J = 7.0$  Hz, 2H), 3.98 (s, 3H), 7.45 (d,  $J = 8.7$  Hz, 2H),  
18 7.67 (d,  $J = 8.3$  Hz, 1H), 8.10 (dd,  $J = 1.9, 8.3$  Hz, 1H), 8.15 (d,  $J$   
19 = 8.7 Hz, 2H), 8.74 (d,  $J = 1.9$  Hz, 1H).

20 Ethyl 4-[[[(5,5-dimethyl-8(7H)-one-5,6-dihydronaphthalen-2-  
21 yl)carbonyl]oxy]benzoate (Compound E44)

22 To a solution of 5,5-dimethyl-5,6-dihydro-8(7H)-one-2-  
23 naphthalenecarboxylic acid (Compound E3, 270.0 mg, 1.24  
24 mmol), ethyl 4-hydroxybenzoate (226.0 mg, 1.364 mmol), 1-(3-  
25 dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (309.0  
26 mg, 1.61 mmol), and 4-*N,N*-dimethylaminopyridine (197.0 mg, 1.61  
27 mmol) in 5.0 mL DMF was stirred at room temperature overnight.  
28 EtOAc (25 mL) was added and the solution washed with H<sub>2</sub>O,

1 1M HCl, and saturated aqueous NaCl before being dried over  
 2 MgSO<sub>4</sub>. Removal of the solvents under reduced pressure and  
 3 column chromatography (7% EtOAc-hexanes) of the residue  
 4 afforded the title compound as a pale-orange solid.

5 <sup>1</sup>H NMR(CDCl<sub>3</sub>): δ 1.41 (t, J = 7.1 Hz, 3H), 1.45 (s, 6H), 2.08 (t,  
 6 J = 6.7 Hz, 2H), 2.80 (t, J = 6.7 Hz, 2H), 4.39 (q, J = 7.1 Hz, 2H),  
 7 7.30 (d, J = 8.7 Hz, 2H), 7.60 (d, J = 8.4 Hz, 1H), 8.13 (d, J = 8.7  
 8 Hz, 2H), 8.31 (dd, J = 1.8, 8.4 Hz, 1H)  
 9 8.04 (d, J = 1.8 Hz, 1H).

10 Ethyl 4-[[[(5,5-dimethyl-8(7H)-anti-(O-methyloxime)-5,6-  
 11 dihydronaphthalen-2-yl)carbonyl]oxy]benzoate (Compound E46)

12 A mixture of ethyl 4-[[[(5,5-dimethyl-8(7H)-one-5,6-  
 13 dihydronaphthalen-2-yl)carbonyl]oxy]benzoate (Compound E44,  
 14 66.0 mg, 0.180 mmol), O-methylhydroxylamine hydrochloride (23.0  
 15 mg, 0.270 mmol), and NaOAc·3H<sub>2</sub>O (62.0 mg, 0.455 mmol) in 3.0  
 16 mL of EtOH was stirred at room temperature for 6 days. The  
 17 reaction was diluted with H<sub>2</sub>O and extracted with EtOAc. The  
 18 combined organic layers were washed with H<sub>2</sub>O and saturated  
 19 aqueous NaCl before being dried over MgSO<sub>4</sub>. Removal of the  
 20 solvents under reduced pressure and column chromatography (4-  
 21 8% EtOAc-hexanes) of the residue, followed by preparative TLC  
 22 (5% EtOAc-hexanes) afforded the title compound.  
 23 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.33 (s, 6H), 1.41 (t, J = 7.1 Hz, 3H), 1.76  
 24 (t, J = 6.9 Hz, 2H), 2.82 (t, J = 6.9 Hz, 2H), 4.03 (s, 3H), 4.39 (q,  
 25 J = 7.1 Hz, 2H), 7.30 (d, J = 8.6 Hz, 2H), 7.50 (d, J = 8.3 Hz,  
 26 1H), 8.11 (dd, J = 1.9, 8.3 Hz, 1H), 8.13 (d, J = 8.6 Hz, 2H), 8.78  
 27 (d, J = 1.9 Hz, 1H).

28 (+/-) Ethyl 2-(1-hydroxy-1,2,3,4-tetrahydro-4,4-dimethyl-7-bromo-

1 naphthalen-1-yl)acetate (Compound E47)

2 To a suspension of Zn (1.20 g, 18.4 mmol) in 10 mL  
3 benzene at 100 °C was slowly added a solution of ethyl 2-  
4 bromoacetate (658.0 mg, 3.94 mmol) and 3,4-dihydro-4,4-dimethyl-  
5 7-bromo-naphthalen-1(2H)-one (Compound G, 500.0 mg, 1.97  
6 mmol) in 20.0 mL benzene. The resulting mixture was heated for  
7 2 h, cooled to room temperature, and the solution decanted from  
8 the residual solids. The solids were washed with EtOAc and the  
9 combined organic layers were washed with cold 15% H<sub>2</sub>SO<sub>4</sub>,  
10 saturated aqueous NaHCO<sub>3</sub>, and saturated aqueous NaCl before  
11 being dried over MgSO<sub>4</sub>. Removal of the solvents under reduced  
12 pressure and column chromatography (10% EtOAc-hexanes)  
13 afforded the title compound as a yellow oil.

14 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.26 (s, 3H), 1.29 (s, 3H), 1.31 (t, J = 7.1  
15 Hz, 3H), 1.62-1.82 (m, 2H), 2.05 (m, 2H), 2.75 (s, 2H), 4.21 (q, J  
16 = 7.1 Hz, 2H), 7.16 (d, J = 8.5 Hz, 1H), 7.33 (dd, J = 2.1, 8.5 Hz,  
17 1H), 7.71 (d, J = 2.1 Hz, 1H).

18 (+/-) Ethyl 2-(1-acetoxy-1,2,3,4-tetrahydro-4,4-dimethyl-7-bromo-  
19 naphthalen-1-yl)acetate (Compound E48)

20 To a solution of (+/-) ethyl 2-(1-hydroxy-1,2,3,4-tetrahydro-  
21 4,4-dimethyl-7-bromo-naphthalen-1-yl)acetate (Compound E47,  
22 200.0 mg, 0.586 mmol) and 4-*N,N*-dimethylaminopyridine (86.0  
23 mg, 0.703 mmol) in 4.0 mL CH<sub>2</sub>Cl<sub>2</sub> at 0 °C was added acetic  
24 anhydride (239.3 mg, 2.344 mmol). The resulting solution was  
25 warmed to room temperature and stirred overnight. The reaction  
26 was warmed to 50 °C for 3 h, cooled to room temperature, and  
27 diluted with EtOAc (70 mL). The solution was washed with H<sub>2</sub>O,  
28 saturated aqueous NaHCO<sub>3</sub>, 10% aqueous HCl, and saturated



1 aqueous NaCl, before being dried over MgSO<sub>4</sub>. Removal of the  
2 solvents under reduced pressure followed by column  
3 chromatography afforded the title compound as a colorless oil.

4 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.23 (t, J = 7.1 Hz, 3H), 1.30 (s, 3H), 1.31  
5 (s, 3H), 1.76 (t, J = 6.9 Hz, 2H), 2.05 (s, 3H), 2.48 (m, 1H), 2.67  
6 (m, 1H), 3.03 (s, 2H), 4.12 (q, J = 7.1 Hz, 2H), 7.19 (d, J = 8.5  
7 Hz, 1H), 7.33 (dd, J = 2.1, 8.5 Hz, 1H), 7.45 (d, J = 2.1 Hz, 1H).

8 (+/-) Ethyl 4-[(5,5-dimethyl-5,6,7,8-tetrahydro-8-acetoxy-8-  
9 carbethoxymethyl-naphthalen-2-yl)carboxamido]-benzoate  
10 (Compound E49)

11 A solution of ethyl 2-(1-acetoxy-1,2,3,4-tetrahydro-4,4-  
12 dimethyl-7-bromo-naphthalen-1-yl)acetate (Compound E48, 450.0  
13 mg, 1.23 mmol), ethyl 4-aminobenzoate (810.0 mg, 4.90 mmol),  
14 1,3-bis(diphenylphosphino)propane (100.0 mg, 0.245 mmol) in 5.0  
15 mL Et<sub>3</sub>N, and 10.0 mL DMSO was sparged with CO (g) for 10  
16 minutes. To this solution was added  
17 bis(triphenylphosphine)palladium(II) chloride (105.0 mg, 0.150  
18 mmol). The solution was placed under 1 atm of CO (balloon) and  
19 heated to 75 °C for 4 days. Upon cooling to room temperature  
20 the mixture was diluted with EtOAc and the solution washed with  
21 10% HCl, H<sub>2</sub>O, and saturated aqueous NaCl before being dried  
22 over Na<sub>2</sub>SO<sub>4</sub>. Removal of the solvents under reduced pressure  
23 and column chromatography (5-25% EtOAc-hexanes) afforded the  
24 title compound.

25 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.20 (t, J = 7.1 Hz, 3H), 1.35 (s, 6H), 1.40  
26 (t, J = 7.1 Hz, 3H), 1.78 (m, 2H), 2.03 (s, 3H), 2.50 (m, 1H), 2.71  
27 (m, 1H), 3.12 (m, 2H), 4.11 (q, J = 7.1 Hz, 2H), 4.37 (q, J = 7.1  
28 Hz, 2H), 7.42 (d, J = 8.2 Hz, 1H), 7.70 (dd, J = 1.9, 8.2 Hz, 1H),

1 7.73 (d,  $J = 8.7$  Hz, 2H), 7.95 (d,  $J = 1.9$  Hz, 1H), 8.04 (d,  $J =$   
 2 8.7 Hz, 2H), 8.20 (s, 1H).

3 Ethyl (E)-4-[(5,5-dimethyl-5,6-dihydro-8(7H)-  
 4 (carbethoxymethylidenyl)-naphthalen-2-yl)carboxamido]-benzoate  
 5 (Compound E50a(*trans*));

6 Ethyl (Z)-4-[(5,5-dimethyl-5,6-dihydro-8(7H)-  
 7 (carbethoxymethylidenyl)-naphthalen-2-yl)carboxamido]-benzoate  
 8 (Compound E50a(*cis*)) and

9 Ethyl (E)-4-[(5,5-dimethyl-5,6-dihydro-8-(carbethoxymethyl)-  
 10 naphthalen-2-yl)carboxamido]-benzoate (Compound E50b)

11 To a solution of (+/-) ethyl 4-[(5,5-dimethyl-5,6,7,8-  
 12 tertahydro-8-acetoxy-8-carbethoxymethyl-naphthalen-2-  
 13 yl)carboxamido]-benzoate (Compound E49, 210.0 mg, 0.438 mmol)  
 14 in 6.0 mL  $\text{CH}_2\text{Cl}_2$  was added 1,8-diazobicyclo[5.4.0]undec-7-ene  
 15 (200.0 mg, 1.314 mmol). The resulting solution was stirred at  
 16 room temperature for 21 h, diluted with EtOAc, and the  
 17 combined solution washed with 10% aqueous HCl and saturated  
 18 aqueous NaCl before being dried over  $\text{MgSO}_4$ . Removal of the  
 19 solvents under reduced pressure and column chromatography  
 20 (15% EtOAc-hexanes) afforded pure (Compound 50b) and a  
 21 mixture of Compound E50a(*trans*) and Compound E50a(*cis*).  
 22 Compound E50a(*trans*) and Compound E50a(*cis*) were isolated  
 23 using reverse phase HPLC (5%  $\text{H}_2\text{O}-\text{CH}_3\text{CN}$ ), each as a colorless  
 24 solid.

25 **Compound E50a(*trans*):**  
 26  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.30 (s, 6H), 1.31 (t,  $J = 7.1$  Hz, 3H), 1.40  
 27 (t,  $J = 7.1$  Hz, 3H), 1.73 (t,  $J = 6.1$  Hz, 2H), 3.21 (t,  $J = 6.1$  Hz,  
 28 2H), 4.16 (q,  $J = 7.1$  Hz, 2H), 4.36 (q,  $J = 7.1$  Hz, 2H), 6.35 (s,

1 1H), 7.46 (d,  $J = 8.1$  Hz, 1H), 7.78 (d,  $J = 8.7$  Hz, 2H), 7.82 (dd,  
2  $J = 1.8, 8.1$  Hz, 1H), 8.04 (d,  $J = 8.7$  Hz, 2H), 8.06 (d,  $J = 1.8$   
3 Hz, 1H), 8.41 (s, 1H).

4 **Compound E50a(cis):**

5  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.31 (t,  $J = 7.1$  Hz, 3H), 1.34 (s, 6H), 1.40  
6 (t,  $J = 7.1$  Hz, 3H), 1.88 (t,  $J = 6.5$  Hz, 2H), 2.61 (t,  $J = 6.5$  Hz,  
7 2H), 4.21 (q,  $J = 7.1$  Hz, 2H), 4.37 (q,  $J = 7.1$  Hz, 2H), 5.92 (t,  $J$   
8  $= 1.1$  Hz, 1H), 7.46 (d,  $J = 8.2$  Hz, 1H), 7.77 (d,  $J = 8.7$  Hz, 2H),  
9 7.88 (dd,  $J = 1.9, 8.2$  Hz, 1H), 8.06 (d,  $J = 8.7$  Hz, 2H), 8.39 (s,  
10 1H).

11 **(Compound E50b):**

12  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.19 (t,  $J = 7.1$  Hz, 3H), 1.28 (s, 6H), 1.39  
13 (t,  $J = 7.1$  Hz, 3H), 2.26 (d,  $J = 4.5$  Hz, 2H), 3.49 (s, 2H), 4.11 (q,  
14  $J = 7.1$  Hz, 2H), 4.38 (q,  $J = 7.1$  Hz, 2H), 5.97 (t,  $J = 4.5$  Hz,  
15 1H), 7.35 (d,  $J = 8.0$  Hz, 1H), 7.70 (dd,  $J = 1.8, 8.0$  Hz, 1h), 7.74  
16 (m, 3H), 8.00 (d,  $J = 8.7$  Hz, 2H), 8.41 (s, 1H).

17 (Z)-4-[(5,5-Dimethyl-5,6-dihydro-8(7H)-(carboxymethylidenyl)-  
18 naphthalen-2-yl)carboxamido]-benzoic acid (Compound E52)

19 A solution of ethyl (Z)-4-[(5,5-dimethyl-5,6-dihydro-8(7H)-  
20 (carbethoxymethylidenyl)-naphthalen-2-yl)carboxamido]-benzoate  
21 (Compound E50a(cis), 15.0 mg, 0.034 mmol) and NaOH (80.0 mg,  
22 2.00 mmol; 2.0 mL of a 1M aqueous solution) in 2.0 mL EtOH  
23 and 1.0 mL THF was stirred overnight at room temperature. The  
24 reaction was quenched by the addition of 10% HCl and extracted  
25 with EtOAc. The combined organic layers were washed with  $\text{H}_2\text{O}$   
26 and saturated aqueous NaCl, and dried over  $\text{Na}_2\text{SO}_4$ . Removal of  
27 the solvents under reduced pressure and crystallization from  
28  $\text{CH}_3\text{CN}$  afforded the title compound as a colorless solid.

<sup>1</sup>H NMR (acetone-d<sub>6</sub>): δ 1.35 (s, 6H), 1.87 (t, *j* = 6.6 Hz, 2H), 2.61 (m, 2H), 5.91 (t, *J* = 1.3 Hz, 1H), 7.55 (d, *J* = 8.3 Hz, 1H), 7.91-8.04 (m, 5H), 8.29 (d, *J* = 1.9 Hz, 1H), 9.66 (s, 1H).

(E)-4-[(5,5-Dimethyl-5,6-dihydro-8(7H)-(carboxymethylidenyl)-naphthalen-2-yl)carboxamido]-benzoic acid (Compound E53)

A solution of ethyl (E)-4-[(5,5-dimethyl-5,6-dihydro-8(7H)-(carbethoxymethylidenyl)-naphthalen-2-yl)carboxamido]-benzoate (Compound E50a(*trans*), 20.0 mg, 0.046 mmol) and NaOH (160.0 mg, 4.00 mmol; 4.0 mL of a 1M aqueous solution) in 3.0 mL EtOH and 1.0 mL THF was stirred overnight at room temperature. The reaction was quenched by the addition of 10% HCl and extracted with EtOAc. The combined organic layers were washed with H<sub>2</sub>O and saturated aqueous NaCl, and dried over Na<sub>2</sub>SO<sub>4</sub>. Removal of the solvents under reduced pressure and crystallization from CH<sub>3</sub>CN afforded the title compound as a colorless solid.

<sup>1</sup>H NMR (acetone-d<sub>6</sub>): δ 1.34 (s, 6H), 1.76 (t, *J* = 6.9 Hz, 2H), 3.24 (m, 2H), 6.46 (t, *J* = 1.8 Hz, 1H), 7.62 (d, *J* = 8.2 Hz, 1H), 7.95-8.05 (m, 5H), 8.29 (d, *J* = 1.9 Hz, 1H), 9.91 (s, 1H).

(+/-) Ethyl 4-[(5,5-dimethyl-8-hydroxy-8-(carbethoxy)-5,6,7,8-tetrahydronaphthalen-2-yl)carbonyl]oxy]benzoate (Compound E54)

To a suspension of Zn (500.0 mg, 7.65 mmol) in 10 mL benzene at 100 °C was slowly added a solution of ethyl 2-bromoacetate (150.3 mg, 0.900 mmol) and ethyl 4-[(5,5-dimethyl-8(7H)-one-5,6-dihydronaphthalen-2-yl)carbonyl]oxy]benzoate (Compound E44, 110.0 mg, 0.300 mmol) in 10.0 mL benzene. The resulting mixture was heated for 2 h, cooled to room temperature, and the solution decanted from the residual solids. The solids

were washed with EtOAc and the combined organic layers washed with cold 15% H<sub>2</sub>SO<sub>4</sub>, saturated aqueous NaHCO<sub>3</sub>, and saturated aqueous NaCl before being dried over MgSO<sub>4</sub>. Removal of the solvents under reduced pressure and column chromatography (15% EtOAc-hexanes) afforded the title compound as a pale-yellow oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.30 (t, J = 7.1 Hz, 3H), 1.33 (s, 3H), 1.37 (s, 3H), 1.43 (t, J = 7.1 Hz, 3H), 1.72-1.90 (m, 2H), 2.11 (m, 2H), 2.84 (m, 2H), 4.23 (q, J = 7.1 Hz, 2H), 4.31 (s, 1H), 4.39 (q, J = 7.1 Hz, 2H), 7.27 (d, J = 8.8 Hz, 2H), 7.46 (d, J = 8.3 Hz, 1H), 8.03 (dd, J = 1.8, 8.3 Hz, 1H), 8.12 (d, J = 8.8 Hz, 2H), 8.43 (d, J = 1.8 Hz, 1H).

Ethyl 4-[[[(5,5-dimethyl-8-(carbethoxy)-5,6-dihydronaphthalen-2-yl)carbonyl]oxy]benzoate (Compound E55)

To a solution of (+/-) ethyl 4-[[[(5,5-dimethyl-8-hydroxy-8-(carbethoxy)-5,6,7,8-tetrahydronaphthalen-2-yl)carbonyl]oxy]benzoate (Compound E54, 35.0 mg, 0.077 mmol) in 10 mL benzene was added a catalytic amount (approximately 2 mg) of *p*-toluenesulfonic acid monohydrate. The solution was heated to reflux under a Dean-Stark trap for 3 h, and then cooled to room temperature and stirred overnight. The solvent was removed under reduced pressure and the title compound isolated from the residue by column chromatography (10% EtOAc-hexanes).

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.21 (t, J = 7.1 Hz, 3H), 1.33 (s, 6H), 1.41 (t, J = 7.1 Hz, 3H), 2.31 (d, J = 4.6 Hz, 2H), 3.54 (s, 2H), 4.14 (q, J = 7.1 Hz, 2H), 4.39 (q, J = 7.1 Hz, 2H), 6.01 (t, J = 4.6 Hz, 1H), 7.28 (d, J = 8.7 Hz, 2H), 7.46 (d, J = 8.1 Hz, 1H), 8.00 (d, J

1 = 1.7 Hz, 1H), 8.04 (dd, J = 1.7, 8.1 Hz, 1H), 8.13 (d, J = 8.7 Hz,  
2 2H).

3 Ethyl 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(R or S)-  
4 tetrahydropyranoxy)-5,5-

5 dimethyl-2-naphthoyloxy]benzoate (Compound E56a) and

6 Ethyl 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(S or R)-  
7 tetrahydropyranoxy)-5,5-

8 dimethyl-2-naphthoyloxy]benzoate (Compound E56b)

9 To a solution of ethyl 4-[5,6,7,8-tetrahydro-8(R or S)-  
10 hydroxy-5,5-dimethyl-2-naphthoyloxy]benzoate (Compound E40, 243  
11 mg, 0.66 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added 3,4-  
12 dihydro-2H-pyran (184 mg, 2.2 mmol) followed by pyridinium p-  
13 toluenesulfonate (26 mg, 0.1 mmol). The reaction mixture was  
14 stirred at ambient temperature for 16 h, and diluted with CH<sub>2</sub>Cl<sub>2</sub>  
15 (20 mL). The mixture was washed successively with water (5  
16 mL), saturated NaHCO<sub>3</sub> (10 mL), water (10 mL) and brine (10  
17 mL). The organic phase was dried over MgSO<sub>4</sub> and then  
18 concentrated *in vacuo* to a pale yellow oil. Purification by flash  
19 column chromatography (silica, 20% EtOAc-hexane) followed by  
20 HPLC separation (partisil 10, 10% EtOAc-hexane) afforded the  
21 title compounds as colorless oil.  
22 Ethyl 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(R or S)-  
23 tetrahydropyranoxy)-5,5-  
24 dimethyl-2-naphthoyloxy]benzoate (Compound E56a)  
25 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.28 (s, 3H), 1.35 (s, 3H), 1.37 (t, J =  
26 7.1Hz, 3H), 1.51-2.11(m, 10H), 3.54-3.61 (m, 1H), 3.96-4.03 (m,  
27 1H), 4.35 (q, J = 7.1Hz, 2H), 4.70 (t, J = 5.0Hz, 1H), 4.87 (t, J =  
28 2.3Hz, 1H), 7.28 (d, J = 8.3Hz, 2H), 7.45 (d, J = 8.2Hz, 1H), 8.02

1 (dd, J = 1.9, 8.3Hz, 1H), 8.10-8.13 (m, 3H).

2 Ethyl 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(S or R)-

3 tetrahydropyranoxy)-5,5-

4 dimethyl-2-naphthoyloxy]benzoate (Compound E56b)

5 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.29 (s, 3H), 1.35 (s, 3H), 1.37 (t, J =

6 7.1Hz, 3H), 1.58-2.10(m, 10H), 3.57-3.63 (m, 1H), 4.01-4.08 (m,

7 1H), 4.35 (q, J = 7.1Hz, 2H), 4.82 (t, J = 4.5Hz, 1H), 4.93 (t, J =

8 3.6Hz, 1H), 7.26 (d, J = 8.3Hz, 2H), 7.44 (d, J = 8.2Hz, 1H), 8.01

9 (dd, J = 1.9, 8.3Hz, 1H), 8.10 (d, J = 8.6Hz, 2H), 8.37 (d, J =

10 1.8Hz, 1H).

11 Ethyl 4-[5,6,7,8-tetrahydro-8(S or R)-(2'(R or S)-

12 tetrahydropyranoxy)-5,5-

13 dimethyl-2-naphthoyloxy]benzoate (Compound E58a) and

14 Ethyl 4-[5,6,7,8-tetrahydro-8(S or R)-(2'(S or R)-

15 tetrahydropyranoxy)-5,5-

16 dimethyl-2-naphthoyloxy]benzoate (Compound E58b)

17 Employing the same general procedure as for the

18 preparation of ethyl 4-[5,6,7,8-tetrahydro-8(R or S)-2(2'(R or S)-

19 tetrahydropyranoxy)-5,5-dimethyl-2-naphthoyloxy]benzoate and

20 ethyl 4-[5,6,7,8-tetrahydro-8(R or S)-2(2'(S or R)-

21 tetrahydropyranoxy)-5,5-dimethyl-2-naphthoyloxy]benzoate, ethyl 4-

22 [5,6,7,8-tetrahydro-8(R or S)-hydroxy-5,5-dimethyl-2-

23 naphthoyloxy]benzoate (Compound E40, 222 mg, 0.6mmol) was

24 converted to a mixture of diastereomers using 3,4-dihydro-2H-

25 pyran (184 mg, 2.2 mmol) and pyridinium p-toluenesulfonate (26

26 mg, 0.1 mmol). Purification by flash column chromatography

27 (silica, 20% EtOAc-hexane) followed by HPLC separation

28 (partisil 10 , 10% EtOAc-hexane) afforded the title compounds as

1 colorless oils.

2 Ethyl 4-[5,6,7,8-tetrahydro-8(S or R)-(2'(R or S)-  
3 tetrahydropyranoxy)-5,5-

4 dimethyl-2-naphthoyloxy]benzoate (Compound E58a):

5 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.29 (s, 3H), 1.35 (s, 3H), 1.37 (t, J =  
6 7.1Hz, 3H), 1.52-2.15(m, 10H), 3.54-3.61 (m, 1H), 3.96-4.03 (m,  
7 1H), 4.35 (q, J = 7.1Hz, 2H), 4.70 (t, J = 5.0Hz, 1H), 4.87 (t, J =  
8 2.3Hz, 1H), 7.26 (d, J = 8.3Hz, 2H), 7.46 (d, J = 8.3Hz, 1H), 8.02  
9 (dd, J = 1.9, 8.3Hz, 1H), 8.10-8.13 (m, 3H).

10 Ethyl 4-[5,6,7,8-tetrahydro-8(S or R)-(2'(S or R)-  
11 tetrahydropyranoxy)-5,5-

12 dimethyl-2-naphthoyloxy]benzoate (Compound E58b)

13 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.32 (s, 3H), 1.35 (s, 3H), 1.37 (t, J =  
14 7.1Hz, 3H), 1.57-2.10(m, 10H), 3.57-3.64 (m, 1H), 4.01-4.08 (m,  
15 1H), 4.35 (q, J = 7.1Hz, 2H), 4.82 (t, J = 4.5Hz, 1H), 4.94 (t, J =  
16 3.6Hz, 1H), 7.26 (d, J = 8.3Hz, 2H), 7.44 (d, J = 8.2Hz, 1H), 8.00  
17 (dd, J = 1.9, 8.3Hz, 1H), 8.10 (d, J = 8.6Hz, 2H), 8.36 (d, J =  
18 1.8Hz, 1H).

19 Benzyl 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(R or  
20 S)tetrahydropyranoxy)-5,5-dimethyl-2-naphthoyloxy]benzoate  
21 (Compound E60a) and  
22 Benzyl 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(S or  
23 R)tetrahydropyranoxy)-5,5-dimethyl-2-naphthoyloxy]benzoate  
24 (Compound E60b)

25 Employing the same general procedure as for the  
26 preparation of ethyl 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(R or S)-  
27 tetrahydropyranoxy)-5,5-dimethyl-2-naphthoyloxy]benzoate and  
28 ethyl 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(S or R)-



1 tetrahydropyranoxy)-5,5-dimethyl-2-naphthoyloxy]benzoate, benzyl  
 2 4-[5,6,7,8-tetrahydro-8(R or S)-hydroxy-5,5-dimethyl-2-  
 3 naphthoyloxy]benzoate (Compound E82, 142 mg, 0.3mmol) was  
 4 converted to a mixture of diastereomers using 3,4-dihydro-2H-  
 5 pyran (184 mg, 2.2 mmol) and pyridinium p-toluenesulfonate (26  
 6 mg, 0.1 mmol). Purification by flash column chromatography  
 7 (silica, 20% EtOAc-hexane) followed by HPLC separation  
 8 (partisil 10 PAC, 10% EtOAc-hexane) afforded the title  
 9 compounds as colorless oil.

10 Benzyl 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(R or  
 11 S)tetrahydropyranoxy)-5,5-dimethyl-2-naphthoyloxy]benzoate  
 12 (Compound 60a)

13  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.30 (s, 3H), 1.37 (s, 3H), 1.54-2.16 (m,  
 14 10H), 3.55-3.63 (m, 1H), 3.98-4.05 (m, 1H), 4.72 (t,  $J = 4.9\text{Hz}$ ,  
 15 1H), 4.89 (t,  $J = 4.6\text{Hz}$ , 1H), 5.39 (s, 2H), 7.28 (d,  $J = 8.6\text{Hz}$ ,  
 16 2H), 7.31-7.50 (m, 6H), 8.03 (dd,  $J = 1.9, 8.3\text{Hz}$ , 1H), 8.12-8.18  
 17 (m, 3H).

18 Benzyl 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(S or  
 19 R)tetrahydropyranoxy)-

20 5,5-dimethyl-2-naphthoyloxy]benzoate (Compound E60b)

21  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.30 (s, 3H), 1.35 (s, 3H), 1.54-2.08 (m,  
 22 10H), 3.57-3.64 (m, 1H), 4.01-4.08 (m, 1H), 4.82 (t,  $J = 4.4\text{Hz}$ ,  
 23 1H), 4.94 (t,  $J = 3.9\text{Hz}$ , 1H), 5.37 (s, 2H), 7.27 (d,  $J = 6.8\text{Hz}$ ,  
 24 2H), 7.34-7.47 (m, 6H), 8.00 (dd,  $J = 2.0, 8.3\text{Hz}$ , 1H), 8.10 (d,  $J =$   
 25  $9.2\text{Hz}$ , 2H), 8.36 (d,  $J = 1.9\text{Hz}$ , 1H).

26 Benzyl 4-[5,6,7,8-tetrahydro-8(S or R)-(2'(R or  
 27 S)tetrahydropyranoxy)-5,5-dimethyl-2-naphthoyloxy]benzoate  
 28 (Compound E62a) and

1 Benzyl 4-[5,6,7,8-tetrahydro-8(S or R)-(2'(S or  
 2 R)]tetrahydropyranoxy)-5,5-dimethyl-2-naphthoyloxy]benzoate  
 3 (Compound E62b)

4 Employing the same general procedure as for the  
 5 preparation of ethyl 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(R or S)-  
 6 tetrahydropyranoxy)-5,5-dimethyl-2-naphthoyloxy]benzoate and  
 7 ethyl 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(S or R)-  
 8 tetrahydropyranoxy)-5,5-dimethyl-2-naphthoyloxy]benzoate, benzyl  
 9 4-[5,6,7,8-tetrahydro-8(R or S)-hydroxy-5,5-dimethyl-2-  
 10 naphthoyloxy]benzoate (Compound E82, 142 mg, 0.3mmol) was  
 11 converted to a mixture of diastereomers using 3,4-dihydro-2H-  
 12 pyran (184 mg, 2.2 mmol) and pyridinium p-toluenesulfonate (26  
 13 mg, 0.1 mmol). Purification by flash column chromatography  
 14 (silica, 20% EtOAc-hexane) followed by HPLC separation  
 15 (partisil 10 PAC, 10% EtOAc-hexane) afforded the title  
 16 compounds as colorless oils. Separation of the diastereomers gave  
 17 a 1:1 ratio of the title compounds both as colorless oils (RT = 32  
 18 minutes and 39 minutes), respectively.

19 Benzyl 4-[5,6,7,8-tetrahydro-8(S or R)-(2'(R or  
 20 S)]tetrahydropyranoxy)-5,5-dimethyl-2-naphthoyloxy]benzoate  
 21 (Compound E62a):

22 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.30 (s, 3H), 1.37 (s, 3H), 1.52-2.15 (m,  
 23 10H), 3.54-3.61 (m, 1H), 3.96-4.03 (m, 1H), 4.70 (t, J = 5.0Hz,  
 24 1H), 4.87 (t, J = 4.5Hz, 1H), 5.37 (s, 2H), 7.26 (d, J = 6.7Hz,  
 25 2H), 7.29-7.49 (m, 6H), 8.02 (dd, J = 1.9, 8.3Hz, 1H), 8.10-8.17  
 26 (m, 3H).

27 Benzyl 4-[5,6,7,8-tetrahydro-8(S or R)-(2'(S or  
 28 R)]tetrahydropyranoxy)-5,5-dimethyl-2-naphthoyloxy]benzoate

1 (Compound E62b):

2  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.30 (s, 3H), 1.35 (s, 3H), 1.54-2.10 (m,  
3 10H), 3.57-3.64 (m, 1H), 4.01-4.08 (m, 1H), 4.82 (t,  $J = 4.7\text{Hz}$ ,  
4 1H), 4.94 (t,  $J = 3.5\text{Hz}$ , 1H), 5.37 (s, 2H), 7.27 (d,  $J = 6.8\text{Hz}$ ,  
5 2H), 7.34-7.47 (m, 6H), 8.00 (dd,  $J = 2.0, 8.3\text{Hz}$ , 1H), 8.10 (d,  $J =$   
6  $9.2\text{Hz}$ , 2H), 8.36 (d,  $J = 1.9\text{Hz}$ , 1H).

7 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(R or S)tetrahydropyranoxy)-5,5-  
8 dimethyl-2-naphthoyloxy]benzoic acid (Compound E64)

9 To a solution of benzyl 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(R  
10 or S)tetrahydropyranoxy)-5,5-dimethyl-2-naphthoyloxy]benzoate  
11 (Compound E60a, 15 mg, 0.03 mmol) in ethyl acetate (5 mL) was  
12 added a catalytic amount of 10% Pd/C. The reaction mixture was  
13 then placed under a blanket of  $\text{H}_2$  by using a  $\text{H}_2$  balloon and  
14 stirred at ambient temperature for 12 h. The reaction mixture was  
15 then filtered through a plug of  $\text{MgSO}_4$  and the filtrate was  
16 concentrated under reduced pressure to give a white solid.  
17 Recrystallization from acetonitrile gave the title compound as a  
18 white solid.

19  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.30 (s, 3H), 1.37 (s, 3H), 1.51-2.17 (m,  
20 10H), 3.57-3.64 (m, 1H), 3.98-4.06 (m, 1H), 4.72 (t,  $J = 4.9\text{Hz}$ ,  
21 1H), 4.90 (t,  $J = 4.6\text{Hz}$ , 1H), 7.31 (dd,  $J = 2.5, 9.3\text{Hz}$ , 2H), 7.48  
22 (d,  $j = 8.3\text{Hz}$ , 1H), 8.04 (dd,  $J = 1.9, 8.3\text{Hz}$ , 1H), 8.13 (d,  $J =$   
23  $1.7\text{Hz}$ , 1H), 8.17 (dd,  $j = 2.4, 9.3\text{Hz}$ , 2H).

24 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(S or R)tetrahydropyranoxy)-5,5-  
25 dimethyl-2-naphthoyloxy]benzoic acid (Compound E65)

26 Employing the same general procedure as for the  
27 preparation of 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(R or  
28 S)tetrahydropyranoxy)-5,5-dimethyl-2-naphthoyloxy]benzoic acid

(Compound E64), benzyl 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(S or R)tetrahydropyranoxy)-5,5-dimethyl-2-naphthoyloxy]benzoate (Compound E60b, 15 mg, 0.03 mmol) was converted to the title compound (white solid).

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.30 (s, 3H), 1.36 (s, 3H), 1.55-2.11 (m, 10H), 3.59-3.64 (m, 1H), 4.02-4.10 (m, 1H), 4.83 (t, J = 5.0Hz, 1H), 4.95 (t, J = 3.7Hz, 1H), 7.29 (d, J = 8.7Hz, 2H), 7.4 (d, J = 8.3Hz, 1H), 8.01 (dd, J = 1.8, 8.2Hz, 1H), 8.16 (d, J = 8.6Hz, 2H), 8.37 (d, J = 2.0Hz, 1H).

4-[5,6,7,8-tetrahydro-8(R or S)-(2'(R or S)tetrahydropyranoxy)-5,5-dimethyl-2-naphthoyloxy]benzoic acid (Compound E66)

Employing the same general procedure as for the preparation of 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(R or S)tetrahydropyranoxy)-5,5-dimethyl-2-naphthoyloxy]benzoic acid (Compound E64), benzyl 4-[5,6,7,8-tetrahydro-8(S or R)-(2'(R or S)tetrahydropyranoxy)-5,5-dimethyl-2-naphthoyloxy]benzoate (Compound E62a, 15 mg, 0.03 mmol) was converted to the title compound (white solid).

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.29 (s, 3H), 1.36 (s, 3H), 1.53-2.15 (m, 10H), 3.56-3.63 (m, 1H), 3.97-4.04 (m, 1H), 4.71 (t, J = 4.9Hz, 1H), 4.89 (t, J = 4.3Hz, 1H), 7.30 (d, J = 8.8Hz, 2H), 7.47 (d, J = 8.4Hz, 1H), 8.03 (dd, J = 1.9, 8.2Hz, 1H), 8.11 (d, J = 2.0Hz, 1H), 8.17 (d, J = 8.6Hz, 2H).

4-[5,6,7,8-tetrahydro-8(S or R)-(2'(S or R)tetrahydropyranoxy)-5,5-dimethyl-2-naphthoyloxy]benzoic acid (Compound E67)

Employing the same general procedure as for the preparation of 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(R or S)tetrahydropyranoxy)-5,5-dimethyl-2-naphthoyloxy]benzoic acid

1 (Compound E64) benzyl 4-[5,6,7,8-tetrahydro-8(S or R)-(2'(S or  
2 R)tetrahydropyranoxy)-5,5-dimethyl-2-naphthoyloxy]benzoate

3 (Compound E62b, 15 mg, 0.03 mmol) was converted to the title  
4 compound (white solid).

5 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.31 (s, 3H), 1.37 (s, 3H), 1.55-2.09 (m,  
6 10H), 3.60-3.65 (m, 1H), 4.04-4.10 (m, 1H), 4.85 (t, J = 4.8Hz,  
7 1H), 4.96 (t, J = 3.8Hz, 1H), 7.31 (d, J = 8.6Hz, 2H), 7.46 (d, J =  
8 8.3Hz, 1H), 8.03 (dd, J = 1.9, 8.2Hz, 1H), 8.18 (d, J = 8.6Hz,  
9 2H), 8.38 (d, J = 1.7Hz, 1H).

10 Ethyl 4-[5,6,7,8-tetrahydro-8(S or R)-(2'(R or  
11 S)tetrahydropyranoxy)-5,5-  
12 dimethylnaphthalene-2-yl]carboxamido]benzoate (Compound  
13 E70a) and

14 Ethyl 4-[5,6,7,8-tetrahydro-8(S or R)-(2'(S or  
15 R)tetrahydropyranoxy)-5,5-  
16 dimethylnaphthalene-2-yl]carboxamido]benzoate (Compound  
17 E70b)

18 Employing the same general procedure as for the  
19 preparation of ethyl 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(R or S)-  
20 tetrahydropyranoxy)-5,5-dimethyl-7-naphthoyloxy]benzoate and ethyl  
21 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(S or R)-tetrahydropyranoxy)-  
22 5,5-dimethyl-7-naphthoyloxy]benzoate, (+/-) ethyl 4-[(5,5-dimethyl-  
23 8-hydroxy-5,6,7,8-tetrahydronaphthalen-2-yl)carboxamido]benzoate  
24 (Compound E32, 142 mg, 0.3mmol) was converted to a mixture of  
25 diastereomers using 3,4-dihydro-2H-pyran (184 mg, 2.2 mmol)  
26 and pyridinium p-toluenesulfonate (26 mg, 0.1 mmol).  
27 Purification by flash column chromatography (silica, 20% EtOAc-  
28 hexane) followed by HPLC separation (partisil 10 PAC, 20%

1 EtOAc-hexane) of the diastereomers gave a 1:1 ratio of the title  
 2 compounds, both as colorless oil (RT = 53 minutes and 60  
 3 minutes), respectively.

4 Ethyl 4-[5,6,7,8-tetrahydro-8(S or R)-(2'(R or  
 5 S)tetrahydropyranoxy)5,5-  
 6 dimethylnaphthalene-2-yl)carboxamido]benzoate (Compound  
 7 E70a):

8 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.24 (s, 3H), 1.30 (s, 3H), 1.34 (t, J =  
 9 7.1Hz, 3H), 1.48-2.10 (m, 10H), 3.52-3.56 (m, 1H), 3.92-3.98 (m,  
 10 1H), 4.30 (t, J = 7.1Hz, 2H), 4.61 (t, J = 4.8Hz, 1H), 4.80 (t, J =  
 11 4.5Hz, 1H), 7.36 (d, J = 8.2Hz, 1H), 7.68-7.74 (m, 3H), 7.80 (d, J  
 12 = 1.9Hz, 1H), 7.98 (d, J = 8.7Hz, 2H), 8.28 (s, 1H).

13 Ethyl 4-[5,6,7,8-tetrahydro-8(S or R)-(2'(S or  
 14 R)tetrahydropyranoxy)5,5-  
 15 dimethylnaphthalene-2-yl)carboxamido]benzoate (Compound  
 16 E70b):

17 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.26 (s, 3H), 1.32 (s, 3H), 1.36 (t, J =  
 18 7.1Hz, 3H), 1.58-2.04 (m, 10H), 3.57-3.61 (m, 1H), 4.00-4.05 (m,  
 19 1H), 4.31 (t, J = 7.1Hz, 2H), 4.78 (t, J = 4.9Hz, 1H), 4.86 (t, J =  
 20 4.6Hz, 1H), 7.37 (d, J = 8.2Hz, 1H), 7.73-7.75 (m, 3H), 8.00-8.03  
 21 (m, 3H), 8.34 (s, 1H).

22 Ethyl 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(R or  
 23 S)tetrahydropyranoxy)5,5-  
 24 dimethylnaphthalene-2-yl)carboxamido]benzoate (Compound  
 25 E72a) and  
 26 Ethyl 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(S or  
 27 R)tetrahydropyranoxy)5,5-  
 28 dimethylnaphthalene-2-yl)carboxamido]benzoate (Compound

1 E72b)

2 Employing the same general procedure as for the  
 3 preparation of ethyl 4-[5,6,7,8-tetrahydro-8-(R or S)-(2'(R or S)-  
 4 tetrahydropyranoxy)-5,5-dimethyl-7-napthoyloxy]benzoate and  
 5 ethyl 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(S or R)-  
 6 tetrahydropyranoxy)-5,5-dimethyl-7-napthoyloxy]benzoate, ethyl 4-  
 7 [5,6,7,8-tetrahydro-8(R or S)-hydroxy-5,5-dimethylnaphthalene-2-  
 8 yl)carboxamido]benzoate (Compound E32, 142 mg, 0.3mmol) was  
 9 converted to a mixture of diastereomers using 3,4-dihydro-2H-  
 10 pyran (184 mg, 2.2 mmol) and pyridinium p-toluenesulfonate (26  
 11 mg, 0.1 mmol). Purification by flash column chromatography  
 12 (silica, 20% EtOAc-hexane) followed by HPLC separation  
 13 (partisil 10 PAC, 20% EtOAc-hexane) afforded the title  
 14 compounds as colorless oil.

15 Ethyl 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(R or  
 16 S)tetrahydropyranoxy)5,5-  
 17 dimethylnaphthalene-2-yl)carboxamido]benzoate (Compound  
 18 E72a):

19 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.25 (s, 3H), 1.32 (s, 3H), 1.35 (t, J =  
 20 7.1Hz, 3H), 1.54-2.10 (m, 10H), 3.53-3.60 (m, 1H), 3.94-4.01 (m,  
 21 1H), 4.31 (t, J = 7.1Hz, 2H), 4.64 (t, J = 4.9Hz, 1H), 4.83 (t, J =  
 22 4.3Hz, 1H), 7.39 (d, J = 8.2Hz, 1H), 7.68-7.73 (m, 3H), 7.80 (d, J  
 23 = 1.8Hz, 1H), 8.01 (d, J = 8.7Hz, 2H), 8.12 (s, 1H).

24 Ethyl 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(S or  
 25 R)tetrahydropyranoxy)5,5-  
 26 dimethylnaphthalene-2-yl)carboxamido]benzoate (Compound  
 27 E72b)

28 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.29 (s, 3H), 1.34 (s, 3H), 1.37 (t, J =

1 7.1Hz, 3H), 1.56-2.10 (m, 10H), 3.58-3.65 (m, 1H), 4.01-4.08 (m,  
 2 1H), 4.33 (t, J = 7.1Hz, 2H), 4.81 (t, J = 4.9Hz, 1H), 4.88 (t, J =  
 3 4.6Hz, 1H), 7.42 (d, J = 8.3Hz, 1H), 7.72-7.78 (m, 3H), 8.02-8.07  
 4 (m, 3H), 8.11 (s, 1H).

5 4-[5,6,7,8-tetrahydro-8(S or R)-(2'(R or S)tetrahydropyranoxy)5,5-  
 6 dimethyl-naphthalene-2-yl)carboxamido]benzoic acid (Compound  
 7 E74)

8 To a solution of ethyl 4-[5,6,7,8-tetrahydro-8(S or R)-(2'(R  
 9 or S)tetrahydropyranoxy)5,5-dimethylnaphthalene-2-  
 10 yl)carboxamido]benzoate (Compound E70a, 54 mg, 0.12 mmol) in  
 11 THF (2 mL) and methanol (1 mL) was added 0.5 M  
 12 lithiumhydroxide (2 mL, 1 mmol). The reaction mixture was  
 13 stirred at ambient temperature for 12 h. The reaction mixture was  
 14 diluted with EtOAc (15 mL), and acidified with 10% HCl to pH 4.  
 15 The organic layer was washed with water (5 mL), brine (10 mL),  
 16 dried (MgSO<sub>4</sub>) and the solvent removed under reduced pressure.  
 17 Recrystallization from EtOAc/hexane afforded the title compound  
 18 as a white solid.

19 <sup>1</sup>H NMR (acetone-d<sub>6</sub>): δ 1.27 (s, 3H), 1.33 (s, 3H), 1.49-2.11 (m,  
 20 10H), 2.80 (br, 1H), 3.51-3.58 (m, 1H), 3.89-3.96 (m, 1H), 4.67 (t,  
 21 J = 4.4Hz, 1H), 4.89 (t, J = 4.5Hz, 1H), 7.52 (d, J = 8.2Hz, 1H),  
 22 7.80 (d, J = 1.9Hz, 1H), 7.91-8.04 (m, 5H), 9.73 (s, 1H).

23 4-[5,6,7,8-tetrahydro-8(S or R)-(2'(S or R)tetrahydropyranoxy)5,5-  
 24 dimethyl-naphthalene-2-yl)carboxamido]benzoic acid (Compound  
 25 E75)

26 Employing the same general procedure as for the  
 27 preparation of 4-[5,6,7,8-tetrahydro-8(S or R)-(2'(R or  
 28 S)tetrahydropyranoxy)5,5-dimethyl-naphthalene-2-



1 yl)carboxamido]benzoic acid (Compound E74) ethyl 4-[5,6,7,8-  
 2 tetrahydro-8(S or R)-(2'(S or R)tetrahydropyranoxy)5,5- dimethyl-  
 3 naphthalene-2-yl)carboxamido]benzoate (Compound E70b, 36 mg,  
 4 0.08 mmol) was converted into the title compound (white solid).  
 5 <sup>1</sup>H NMR (acetone-d<sub>6</sub>): δ 1.28 (s, 3H), 1.34 (s, 3H), 1.51-2.02 (m,  
 6 10H), 2.80 (br, 1H), 3.55-3.60 (m, 1H), 3.96-4.03 (m, 1H), 4.77 (t,  
 7 J = 5.4Hz, 1H), 4.92 (t, J = 3.8Hz, 1H), 7.50 (d, J = 8.3Hz, 1H),  
 8 7.82 (dd, J = 2.0, 8.3Hz, 1H), 7.97-8.02 (m, 4H), 8.09 (d, J =  
 9 1.9Hz, 1H), 9.77 (s, 1H).

10 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(R or S)tetrahydropyranoxy)5,5-  
 11 dimethyl-naphthalene-2-yl)carboxamido]benzoic acid (Compound  
 12 E76)

13 Employing the same general procedure as for the  
 14 preparation of 4-[5,6,7,8-tetrahydro-8(S or R)-(2'(R or  
 15 S)tetrahydropyranoxy)-5,5-dimethyl-naphthalene-2-  
 16 yl)carboxamido]benzoic acid (Compound E74), ethyl 4-[5,6,7,8-  
 17 tetrahydro-8(R or S)-(2'(S or R)tetrahydropyranoxy)5,5- dimethyl-  
 18 naphthalene-2-yl)carboxamido]benzoate (Compound E72b, 36 mg,  
 19 0.08 mmol) was converted into the title compound (white solid).  
 20 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.28 (s, 3H), 1.34 (s, 3H), 1.55-2.08 (m,  
 21 10H), 3.59-3.65 (m, 1H), 4.04-4.12 (m, 1H), 4.82 (t, J = 4.9Hz,  
 22 1H), 4.88 (t, J = 2.6Hz, 1H), 7.43 (d, J = 8.3Hz, 1H), 7.74-7.81  
 23 (m, 3H), 8.02 (d, J = 1.8Hz, 1H), 8.06 (d, J = 8.7Hz, 2H), 8.30 (s,  
 24 1H).

25 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(S or R)tetrahydropyranoxy)5,5-  
 26 dimethyl-naphthalene-2-yl)carboxamido]benzoic acid (Compound  
 27 E77)

28 Employing the same general procedure as for the

1 preparation of 4-[5,6,7,8-tetrahydro-8(S or R)-(2'(R or  
 2 S)tetrahydropyranoxy)5,5-dimethyl-naphthalene-2-  
 3 yl)carboxamido]benzoic acid (Compound E74), ethyl 4-[5,6,7,8-  
 4 tetrahydro-8(R or S)-(2'(S or R)tetrahydropyranoxy)5,5- dimethyl-  
 5 naphthalene-2-yl)carboxamido]benzoate (Compound E72a, 36 mg,  
 6 0.08 mmol) was converted into the title compound (white solid).  
 7 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.27 (s, 3H), 1.34 (s, 3H), 1.55-2.13 (m,  
 8 10H), 3.57-3.63 (m, 1H), 3.97-4.03 (m, 1H), 4.70 (t, J = 4.7Hz,  
 9 1H), 4.89 (t, J = 2.4Hz, 1H), 7.44 (d, J = 8.3Hz, 1H), 7.72-7.77  
 10 (m, 3H), 7.82 (d, J = 1.9Hz, 1H), 8.06-8.10 M, 3H).

11 5,5-dimethyl-5,6-dihydro-8-(1,1-dimethylethyl)-2-  
 12 naphthalenecarboxylic acid (Compound E78)

13 A solution of 7-bromo-1-(1,1-dimethylethyl)-3,4-dihydro-  
 14 4,4-dimethylnaphthalene (Compound C42, 450.0mg, 1.54 mmol)  
 15 in 20 mL of THF was cooled to -78 °C and 197.3 mg (3.08 mmol;  
 16 1.8 mL of a 1.7M solution in pentane) added giving a pale-yellow  
 17 solution. After 1h, CO<sub>2</sub> (from evaporation of Dry Ice, dried with  
 18 CaSO<sub>4</sub>) was bubbled through the solution for 1h. After stirring at  
 19 -78 °C for an additional hour, the reaction was quenched with  
 20 10% aqueous HCl. The solution was extracted with EtOAc and  
 21 the combined organic layers washed with H<sub>2</sub>O and saturated  
 22 aqueous NaCl before being dried over Na<sub>2</sub>SO<sub>4</sub>. Removal of the  
 23 solvents under reduced pressure, and washing of the residue with  
 24 hexanes afforded the title compound as a colorless solid.  
 25 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 1.25 (6H, s), 1.38 (9H, s), 2.17 (2H, d, J =  
 26 4.9 Hz), 6.02 (1H, t, J = 4.9 Hz), 7.41 (1H, d, J = 8.1 Hz), 7.91  
 27 (1H, dd, J = 1.6, 8.1 Hz), 8.42 (1H, d, J = 1.6 Hz).

28 Ethyl 4-[(5,5-dimethyl-5,6-dihydro-8-(1,1-dimethylethyl)-2-

1 naphthalenyl)carboxamido]-benzoat (Compound E79)

2 A solution of 5,5-dimethyl-5,6-dihydro-8-(1,1-dimethylethyl)-  
3 2-naphthalenecarboxylic acid (Compound E78, 150.0 mg, 0.581  
4 mmol), ethyl 4-aminobenzoate (115.2 mg, 0.697 mmol), 1-(3-  
5 dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (145.0  
6 mg, 0.755 mmol), and 4-*N,N*-dimethylaminopyridine (89.0 mg,  
7 0.697 mmol) in 8.0 mL DMF was stirred overnight at room  
8 temperature. EtOAc (110 mL) was added and the solution  
9 washed with H<sub>2</sub>O, 5% HCl, saturated aqueous NaHCO<sub>3</sub>, and  
10 saturated aqueous NaCl before being dried over MgSO<sub>4</sub>.

11 Removal of the solvents under reduced pressure and column  
12 chromatography (10-25% EtOAc-hexanes) of the residual oil  
13 afforded the title compound as a colorless solid.

14 <sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 1.25 (6H, s), 1.39 (9H, s), 1.40 (3H, t, J = 7.1  
15 Hz), 2.18 (2H, d, J = 4.9 Hz), 4.37 (2H, q, J = 7.1 Hz), 6.05 (1H,  
16 t, J = 4.9 Hz), 7.41 (1H, d, J = 8.0 Hz), 7.58 (1H, dd, J = 1.8, 8.0  
17 Hz), 7.24 (2H, d, J = 8.7 Hz), 7.91 (1H, s, ), 8.06 (2H, d, J = 8.7  
18 Hz), 8.26 (1H, d, J = 1.8 Hz).

19 4-[(5,5-dimethyl-5,6-dihydro-8-(1,1-dimethylethyl)-2-  
20 naphthalenyl)carboxamido]-benzoic acid (Compound E80)

21 To a solution of ethyl 4-[(5,5-dimethyl-5,6-dihydro-8-(1,1-  
22 dimethylethyl)-2-naphthalenyl)carboxamido]-benzoate (Compound  
23 E79, 50.0 mg, 0.123 mmol) in 2.0 mL of EtOH and 3.0 mL THF  
24 was added NaOH (240.0 mg, 6.00 mmol; 3.0 mL of a 2N aqueous  
25 solution). After stirring overnight at room temperature the  
26 reaction was quenched by the addition of 1M aqueous HCl. The  
27 mixture was extracted with EtOAc and the combined organic  
28 layers washed with H<sub>2</sub>O and saturated aqueous NaCl before being

1 dried over  $\text{Na}_2\text{SO}_4$ . Removal of the solvents under reduced  
 2 pressure afforded the title compound as a colorless solid.  
 3  $^1\text{H}$  NMR( $\text{d}_6$ -acetone)  $\delta$  1.24 (6H, s), 1.38 (9H, s), 2.17 (2H, d, J =  
 4 4.9 Hz), 6.08 (1H, t, J = 4.9 Hz), 7.45 (1H, d, J = 8.1 Hz), 7.81  
 5 (1H, dd, J = 1.8, 8.1 Hz), 7.97 - 8.05 (4H, m), 8.31 (1H, d, J = 1.8  
 6 Hz).

7 Benzyl-4-[[5,5-dimethyl-5,6,7,8-tetrahydro-8-oxo-naphthalen-2-  
 8 yl)carbonyl]oxy]-benzoate (Compound E81)

9 To a solution of 5,5-dimethyl-5,6,7,8-tetrahydro-8-oxo-  
 10 naphthalen-2-carboxylic acid (Compound E3, 386 mg, 1.77 mmol)  
 11 in dimethylformamide (4 mL) was added 1-(3-  
 12 dimethylaminopropyl)-3-ethylcarboimide hydrochloride (440 mg,  
 13 2.3 mmol) followed by dimethylamino pyridine (DMAP) (280 mg,  
 14 2.3 mmol). The mixture was stirred for 10 minutes, and benzyl 4-  
 15 hydroxy benzoate (426 mg, 1.9 mmol) was added and stirred at  
 16 ambient temperature for 16 hours. The mixture was diluted with  
 17 ethyl acetate (100 mL) and washed with water (10 mL), brine (10  
 18 mL), dried and solvent distilled off. The title compound was  
 19 obtained as a pale yellow solid after chromatographic purification.  
 20  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.42 (s, 6H), 2.05 (t, J = 6.7 Hz, 2H), 2.77 (t,  
 21 J = 6.7 Hz, 2H), 5.37 (s, 2H), 7.25-7.50 (m, 7H), 7.58 (d, J = 8.3  
 22 Hz, 1H), 8.15 (d, J = 8.1 Hz, 2H), 8.28 (dd, J = 1.9, 8.3 Hz, 1H),  
 23 8.82 (d, J = 1.9 Hz, 1H).

24 Benzyl-4-[[5,5-dimethyl-5,6,7,8-tetrahydro-8-hydroxy-naphthalen-2-  
 25 yl)carbonyl]oxy]-benzoate (Compound E82)

26 To a solution of benzyl-4-[[5,5-dimethyl-5,6,7,8-tetrahydro-8-  
 27 oxo-naphthalen-2-yl)carbonyl]oxyl]-benzoate ((Compound E81, 377  
 28 mg, 0.88 mmol) in dimethoxyethane (20 mL) was added

1 sodiumborohydride (33 mg, 0.9 mmol). The mixture was stirred  
2 for 12 hours at room temperature. The mixture was diluted with  
3 ethylacetate (50 mL), washed with water (10 mL), brine (10 mL),  
4 dried and solvent distilled off. The title compound was obtained  
5 as a white solid after chromatographic purification.  
6  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.30 (s, 3H), 1.37 (s, 3H), 1.60-1.75 (m, 1H),  
7 1.85-2.00 (m, 2H), 2.05-2.20 (m, 1H), 2.30 (brs, 1H), 4.81 (t, J =  
8 5.6, 1H), 5.38 (s, 2H), 7.27 (d, J = 8.7 Hz, 2H), 7.35-7.51 (m, 6H),  
9 8.04 (dd, J = 1.9, 8.3 Hz, 1H), 8.15 (d, J = 8.7 Hz, 2H), 8.31 (d, J  
10 = 1.9 Hz).